PREVENTION OF TYPE 2 DIABETES IN PEOPLE LIVING WITH HIV UNDERSTANDING RISK FACTORS, AND INVESTIGATING THE EFFECTIVENESS AND ACCEPTABILITY OF A LIFESTYLE INTERVENTION

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PREVENTION OF TYPE 2 DIABETES IN PEOPLE LIVING WITH HIV:

UNDERSTANDING RISK FACTORS, AND INVESTIGATING THE EFFECTIVENESS AND ACCEPTABILITY OF A LIFESTYLE INTERVENTION

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A Thesis Submitted to King's College London

for the Degree of Doctor of Philosophy

in the Faculty of Life Sciences and Medicine

The Division of Immunology, Infection and Inflammatory Disease

King's College London

June 2016

Dedication

For my Mum, Maisie.

Publications

Published Abstracts:

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Thesis Abstract

People living with HIV have up to a fourfold probability of developing type 2 diabetes (T2D), driven by HIV-related factors including the direct effect of certain HIV medicines, and general factors, notably obesity and age. This mixed-methods research, studying HIV patients in South London, aimed to characterise risk factors for T2D, and investigate the effectiveness and acceptability of a pilot lifestyle intervention.

Data from a cross-sectional study (n=338) showed a T2D prevalence of 15.1%. Rather than HIV-specific factors the greater contribution to risk of prediabetes/T2D were the conventional risk factors hepatic steatosis and hypertension (odds ratios 7.3 and 2.6 respectively); modifiable factors made a greater contribution to prediabetes/T2D than fixed or historic factors.

A pilot diet and activity intervention for people with HIV and prediabetes (n=33) demonstrated statistically significant improvements in 6-month change in glucose and insulin for both fasting levels (5.5% and 23.6% reductions respectively) and postprandial 3-hour incremental area under the curve (17.6% and 31.4% reductions respectively), and significant reductions in mean values for weight (4.7%), waist (6.2%), systolic blood pressure (7.7%) and fasting triglycerides (36.2%).

Qualitative interviews (n=23) identified key themes of confidentiality and fear of disclosure of HIV status. Those who declined participation or achieved fewer intervention goals exhibited an external health locus of control, blaming diabetes risk on HIV medicines. Those who achieved more goals prioritised treating prediabetes. Enablers included a desire to avoid adding to pill or disease burden, and a strong support network. Deliberate weight loss leading to loss of cultural identity and disclosure of HIV status were significant barriers.

T2D is highly prevalent in HIV. The effectiveness of the pilot intervention demonstrates the potential to prevent or delay T2D in HIV. However, people living with HIV present with unique barriers to change; future interventions must address these to improve effectiveness.

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Abbreviations

ADA	American Diabetes Association
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
ARV	Antiretroviral
AUC	Area Under the Curve
BIA	Bioelectrical Impedance Analysis
BHIVA	British HIV Association
BME	Black and Minority Ethnic
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BP	Blood Pressure
CBT	Cognitive Behavioural Therapy
COM-B	Capability, Opportunity, Motivation – Behaviour Change
CALO_RE	Coventry, Aberdeen and London - Refined
CHO	Carbohydrate
CI	Confidence Intervals
CREATE	The Cardiovascular Risk Evaluation and Antiretroviral Therapy Effects Study
CRF	Clinical Research Facility
CVD	Cardiovascular Disease
D:A:D	The Data Collection on Adverse Events of Anti-HIV Drugs Study
DASH	Dietary Approaches to Stop Hypertension
DPP	Diabetes Prevention Programme
DPS	Diabetes Prevention Study
EACS	European AIDS Clinical Society
ESPEN	European Society for Parenteral and Enteral Nutrition
FRS	Framingham Risk Score
FSLMTT	Frequently Sampled Liquid Meal Tolerance Test
FSOGTT	Frequently Sampled Oral Glucose Tolerance Test
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GLUT-4	Glucose Transport Type 4
HAART	Highly Active Antiretroviral Therapy
HAT-QoL	HIV/AIDS Targeted Quality of Life Instrument
HbA1c	Glycated Haemoglobin
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIEC	Hyperinsulinaemic-euglycaemic clamp
HIV	Human Immunodeficiency Virus
HOMA-IR	Homoeostatic Model of Assessment of Insulin Resistance
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IPA	Interpretive Phenomenological Analysis
IPAQ	International Physical Activity Questionnaire
IQR	Inter Quartile Range

IR	Insulin Resistance
JBS	Joint British Societies (cardiovascular disease and hypertension)
KHP	King's Health Partners
LBM	Lean Body Mass
LDL	Low Density Lipoprotein
LMTT	Liquid Meal Tolerance Test
MET	Metabolic Equivalent
MI	Myocardial Infarction
MOS-HIV	HIV Medical Outcomes Survey
MRC	Medical Research Council
MUFA	cis-Monounsaturated fatty acids
NADC	Non-AIDS Defining Cancer
NCEP	National Cholesterol Education Programme
NIHR	National Institute for Health Research
NMES	Non-Milk Extrinsic Sugars
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSEC	National Socioeconomic Classification
NSP	Non-starch Polysaccharide
OGIS	Oral Glucose Sensitivity Index
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PA	Physical Activity
PI	Protease Inhibitor
PLWH	People Living with HIV
PPAR-ɣ	Peroxisome proliferator-activated receptor gamma
PPI	Patient Public Involvement
PUFA	Polyunsaturated Fatty Acids
QUICKI	Qualitative Insulin Sensitivity Check Index
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Risk Ratio
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	Standard Error of the Mean
SFA	Saturated Fatty Acids
STOP	The Study To Prevent Type 2 Diabetes in HIV
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TDF	Theoretical Domains Framework
TEE	Total Energy Expenditure
TG	Triglyceride
TNF-α	Tumour Necrosis Factor Alpha
UNAIDS	The Joint United Nations Organisation on HIV and AIDS
VL	Viral Load (HIV)
VLDL	Very Low Density Lipoprotein
WHO	World Health Organisation

Acknowledgements

I was would like to thank my principal supervisors Dr Barry Peters and Dr Louise Goff, who provided constant encouragement, challenge and support throughout. Their complementary experience, sage advice and motivational approach proved invaluable, sharing excitement at emerging results from data analysis. My clinical supervisor Dr Tony Wierzbicki cheerfully provided his encyclopaedic knowledge and realistic views. I would like to thank Dr Carol Rivas who patiently guided and encouraged me in my first experiences of conducting in-depth qualitative research.

The clinical and research staff in HIV outpatients at St Thomas' and King's College Hospitals provided support and encouragement throughout recruitment. I would like to thank the staff at the Clinical Research Facility at St. Thomas' Hospital, the BioBank at Guy's Hospital, and the academic and research staff at King's College London. My dietetic colleagues at Guy's and St. Thomas' Hospital were enormously supportive during the application for this Fellowship, and throughout the research project.

I would like to thank my PhD supervising committee Stipo Jurcevic, Hendrik Huthoff, Stephen Thomas and Judy Lawrence, who were all supportive, positively critical and challenging.

I am grateful to the NIHR for funding the research fellowship that made this PhD possible.

Patient representatives Juliet Bosa and Len Hughes, members of the HIV and Diabetes peer support group, and Simon Collins from i-Base provided insight, support and encouragement at all stages.

A huge thanks goes to the patients who were involved in this research: those who listened patiently to my proposal to participate in the study but declined to take part, those who wanted to take part but were unfortunately excluded, and the 340 who cheerfully consented to let me experiment on them. I would like to single out special thanks for the 33 people who shared the six-month intervention journey with me, and the 23 who trusted me with their personal stories at interview.

Thanks goes to Kate Barker for design advice, Tessa Kendall for interview transcription and proof reading, and Nick Parsons for words of wisdom, encouragement and pastoral support.

I would like to thank my dad Jim and all of my family and friends for their steadfast interest, support and understanding, particularly when this work limited participation in the important stuff.

Finally, Gareth, thank you for the constancy of your love, encouragement, support, straight-talking and sacrifice. You held my hand.

Statement of Contribution

Conception of Study

I conceived the idea of developing an investigation into the phenotype and prevention of type 2 diabetes in people living with HIV.

Study Design and Delivery

I led the design of the study. Drs Barry Peters and Louise Goff provided guidance and advice. The Research Design Service advised on the feasibility and academic potential of the project prior to applying to the NIHR Fellowship scheme. Dr Carol Rivas provided oversight on the design of the qualitative study. I convened an advisory meeting comprised of expert patients and scientists living with HIV who provided opinion on study design.

I was responsible for the ethics application, with Drs Peters and Goff providing guidance. As principal investigator I was solely responsible for, and performed the day to day delivery of, all parts of the study including developing risk assessments, standard operating procedures and data collection forms, recruitment, screening, and management of participants, laboratory processing of blood samples, routine and adverse event reporting, and clinical handover of participants at point of exit from the study. Patient representative Juliet Bosa raised awareness of the study among peers.

Phenotype of Type 2 Diabetes in HIV

I performed data collection for 332 participants, and Mr Damon Nicholls for 6 participants. I analysed data, with guidance from Drs Peters and Goff, and an advice appointment with a KCL Statistician. I supervised two medical students Jon Mok and Peter Killeen who calculated 10 year diabetes and CVD risk, and three nutrition MSc students, Georgina Murphy, Roseanna Henderson, and Hannah Partridge who analysed 157 diet diaries; I analysed the remainder.

Diet and Physical Activity Intervention

I delivered the intervention. A Clinical Research Facility (CRF) nurse performed phlebotomy, and assisted with clinical care during the liquid meal tolerance test. I processed blood samples in the CRF laboratory, managed freezer storage and organised transfer for analysis. Ms Tracy Dew analysed samples for insulin, glucose and incretin hormones, and the Guy's and St. Thomas' lab analysed samples for lipids and HbA1c. I analysed data, with advice from Drs Peters and Goff, and an advice appointment with a KCL Statistician.

Qualitative Study

I interviewed the participants. I transcribed the first six interviews; subsequent interview recordings were transcribed by Tessa Kendall. I analysed data thematically, and produced a synthesis of results with Drs Rivas and Goff providing advice and oversight.

1 INTRODUCTION

> *'unless better prevention can be achieved, between 2016 and 2026 as many as 15,000 new HIV-associated type 2 diabetes diagnoses may present in the UK'*

1.1 Background

This thesis describes a portfolio of research investigating the relationship between human immunodeficiency virus (HIV) and type 2 diabetes (T2D). People living with HIV (PLWH) in the United Kingdom (UK) form the focus of this research, investigating areas for which there is a paucity of published evidence: the phenotype of prediabetes and T2D in this cohort and how this has changed over the last 10 years; the effectiveness and acceptability of preventing T2D in PLWH presenting with prediabetes; and characterising enablers and barriers to diet and physical activity change, some of which are specific to PLWH.

Elsewhere, investigators have conducted prospective observational and cross-sectional studies characterising incidence, prevalence and factors associated with T2D in HIV in cohorts outside of the UK. I present these in a literature review in Section 1.5.2, page 38.

PLWH and T2D face particular challenges. T2D has been reported to be up to four times more prevalent among PLWH matched to HIV negative individuals for age, ethnicity and body mass index (BMI). The screening for, and management of, T2D in HIV present distinct challenges, as antiretroviral (ARV) medications can result in underestimation of glycated haemoglobin and can interact with hypoglycaemic agents leading to the necessity of dose adjustment. HIV patients with T2D may have a poorer response to diabetes treatments compared to matched HIV negative individuals. And, finally, to date no HIV-specific diabetes screening or treatment guidelines have been developed in the UK, Europe, USA and other regions.

Despite these challenges to date no investigators have compared how factors associated with T2D in HIV may have changed over time, or estimated the relative contribution of modifiable and fixed factors. Additionally there is no published data regarding the uniquely diverse HIV cohort in the UK. The few studies that have investigated the effect of lifestyle change on markers of insulin resistance in PLWH employed support too intensive to be applied widely in clinical practice, and demonstrated either an absence of or a small effect size.

In this thesis I have presented background information on both HIV and type 2 diabetes, with reviews of prevention of T2D through changes in diet and physical activity. I have then presented a summary of issues facing people living with both conditions. The Introduction concludes with a discussion of my epistemological stance and how this frames my approach to this project, and finally I have presented an overview of design, research hypotheses, and aims and objectives.

I have discussed choice of methodology, described procedures and presented results of three inter-related studies:

1. In the phenotype study I have aimed to delineate how the prevalence of dysglycaemia (prediabetes and T2D itself) has changed over time, and to investigate which factors drive these changes. Methodology and results are presented in sections 2.5 and 3.1
2. The findings from a pilot diet and lifestyle intervention are presented in Section 3.3. I have described lifestyle interventions in HIV patients in the literature review, but to date no lifestyle intervention to specifically impact insulin resistance in this patient group has been published. The intention for this pilot intervention was to investigate the effectiveness of an individualised approach on markers of insulin resistance, based on proven diabetes prevention trials
3. I have presented the methods and results of a qualitative investigation in sections 2.7 and 3.4 respectively. Enablers and barriers to diet and activity change in PLWH, some of which are HIV-specific, have been characterised by other investigators in a peripheral manner only

Finally, in the discussion and conclusion I have presented key findings, weighed up strengths and limitations of the research, and discussed implications for clinical practice and future research.

1.2 Genesis of the Project: a Personal Perspective

Shortly after I commenced work as a specialist dietitian in the HIV clinic at St. Thomas' Hospital in 1998 we set up a multidisciplinary metabolic clinic for HIV outpatients. This was in response to the developing need to treat patients experiencing body shape changes (lipodystrophy). At this time there appeared to be an association between certain ARVs and metabolic abnormalities including dysglycaemia (Kilby and Tabereaux, 1998). The use of those ARVs was largely discontinued, however there remained a legacy of toxicities for some of the patients who had been exposed to them. Patients presenting with T2D were otherwise few, unsurprising given the relatively young age and modest BMI of the cohort. However, by 2010 a pattern emerged where patients recently diagnosed with T2D electively attended for advice from the HIV specialist dietitians. Patients reported GPs prescribing medication to control dysglycaemia, only to be told later in HIV outpatients that these medicines may negatively interact with their HIV treatment. Faced with suboptimal therapy for their T2D, patients were seeking advice to modify lifestyle factors. At this time dietitians in HIV care began discussing as yet unpublished observations of HIV-specific barriers to changing diet and physical activity. For example some overweight patients reported fear of deliberate weight loss, believing this might accidentally disclose HIV status to family and friends.

In January 2012 an HIV article was published in the national diabetes magazine Balance (Flagg et al., 2012), discussing for the first time in the UK challenges facing PLWH and diabetes comorbidity. At a patient forum meeting shortly after, HIV patients, interested members of the public and HIV science advocates suggested that given potentially suboptimal treatment of T2D in PLWH, the focus of any future research should be diabetes prevention. They felt it was important that this research should reflect their diversity, and in particular recruit women, people from Black and Minority Ethnic groups (BME) and older people.

These views informed the design of the research presented in this thesis. The project was funded by the National Institute for Health Research (NIHR) as part of a Clinical Doctoral Research Fellowship. Patient and public involvement continued to inform the ongoing development of the work. The research programme commenced in June 2012, with the final participant completing the study in October 2015.

1.3 HIV

1.3.1 HIV: History and Prevalence

The HIV epidemic continues to develop. In 2014 2.0 million people were diagnosed with HIV increasing the estimated global prevalence to 36.9 million (UNAIDS, 2015). Despite the widespread introduction of successful antiretroviral therapy the predicted HIV-related mortality rate for 2015 is 1.7 million. The World Health Organisation (WHO) has a stated aim that by 2020 goals to treat 90% of PLWH with ARVs will significantly reduce transmission, morbidity and mortality (World Health Organisation, 2015).

HIV was first identified in 1983 although more recently isolation of the virus from earlier preserved tissue samples has led to the theory that HIV evolved from a simian retrovirus in Africa sometime around the start of the 20th century (Maartens et al., 2014). In 1981 the United States Centre for Disease Control was made aware of a rare pneumonia caused by Pneumocystis jirovecii (previous nomenclature Pneumocystis carinii) in five gay men who presented with a concomitant suppressed CD4 T-cell count resulting in a deficit in cell-mediated immunity (Gottlieb et al., 1981). The link between the development of profound immunodeficiency and the retrovirus HIV was made and the term acquired immune deficiency syndrome (AIDS) was used to describe this. AIDS presents with wasting: protein energy malnutrition. In Africa those with AIDS were referred to as having “slim disease”, and for many people an enduring image of a person ill with HIV is someone experiencing severe undernutrition (Maartens et al., 2014). In the late 1990s use of highly active antiretroviral therapy (HAART) became widespread, where two or more ARVs are used in combination to suppress viral replication allowing immune reconstitution. Its widespread use in recent years has led to HIV becoming, for those able to access treatment, a chronic manageable condition, with dramatic reductions in morbidity and mortality. Transmission of HIV continues with over 2 million testing positive worldwide each year. Despite best efforts vaccines for both prevention and treatment continue to prove elusive. Although vaccine research continues, to combat ongoing transmission of HIV the World Health Organisation has released guidelines that all PLWH should be treated with HAART irrespective of degree of immunosuppression (World Health Organisation, 2015). Taken as a whole, the cohort of PLWH is an ageing population as survival radically improves.

Table 1.1: UK Regional HIV Prevalence and Ethnicity Data, 2014

	White	Black Caribbean	Black African	Black Other	South Asian	Other / Not known	Total
London (%)	16,860 (47.7%)	1,790 (5.1%)	11,335 (32.1%)	1,134 (3.2%)	785 (2.2%)	4,068 (11.5%)	35,363
England Total	40,947	2,624	25,679	1,742	1,423	5,902	78,317
UK Total	46,310	2,649	27,017	1,779	1,462	6,383	85,489

Source: Public Health England, 2015

In the UK over 85,000 people are known to be living with HIV (Table 1.1). Another 25,000 are estimated to be HIV positive and unaware of their status (Public Health England, 2015a). Given the history of the epidemic, two groups make up the largest part of the cohort: gay men, the majority of whom are White, and Black Africans resident in the UK. Non-White ethnicities comprise the majority of Londoners living with HIV. HIV incidence in the UK remains stable, with around 6,200 new HIV positive diagnoses per year. The area in the UK with both the highest incidence and highest prevalence is South East London, where the majority of patients who participated in the current research reside. Here the incidence of HIV continues at a steady annual rate of approximately 600 cases, whereas the diagnosis of AIDS and HIV-related death rates have both declined rapidly to less than 30 cases each per year.

HAART consists of two or more ARVs used in combination, each targeting different sites in the viral replication pathway. Adherence is vital to prevent viral resistance and can prove challenging, especially when medications must be taken with or without food and within certain time windows (Maartens et al., 2014). For these reasons the risks and benefits of switching from one ARV to another is cautiously considered, although this can remain a treatment option. Following the WHO guidelines, the British HIV Association (BHIVA) revised guidelines recommend that all HIV patients should be treated with HAART irrespective of disease progression or degree of immunosuppression (Churchill et al., 2015).

Stigma associated with HIV infection remains prevalent and can lead to negative attitudes, prejudice, discrimination, and psychological damage. This stigma may stem from incorrect beliefs regarding behaviours associated with HIV transmission, onward transmission of the virus itself, and disease progression. People living with HIV can self-isolate as a result, and rates of poor mental health are high, with up to 50% reporting a current or past psychiatric disorder (Blashill et al., 2011).

1.3.2 The Metabolic Consequences of HIV Infection

Both HIV infection and antiretroviral therapy may lead to an array of long-term metabolic changes (Table 1.2), of which T2D is one, and is discussed in more detail in Section 1.5. Prior to the development of effective ARVs metabolic changes were observed as HIV infection progressed, thought to be associated with inflammation and cytokine disturbance. These changes included futile cycling of triglycerides and hypogonadism (testosterone deficiency). More recently, it has become apparent that ARVs used to treat HIV can lead to a range of chronic metabolic complications, including redistribution of subcutaneous fat (lipodystrophy) and dyslipidaemia, and increased risk or accelerated development of non-communicable conditions associated with ageing including osteoporosis, cognitive decline, cardiovascular disease, stroke, chronic kidney disease, non AIDS-defining cancers and importantly for the research presented in this thesis, type 2 diabetes.

Investigators leading the large international prospective multi-cohort Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study (n=33,308) found a 42% prevalence of metabolic syndrome (Worm et al., 2010). In the UK the Cardiovascular Risk Evaluation and Antiretroviral Therapy Effects (CREATE) study investigators (Aboud et al., 2010, Elgalib et al., 2011) characterised demographics, anthropometry, biochemistry, HIV and ARV history, medication use and cardiovascular risk factors for 1,021 patients recruited from outpatient clinics in South London. In this cohort, modifiable cardiometabolic risk factors, specifically overweight, hypertension, hyperlipidaemia and smoking, contributed to the majority of the risk of subsequent disease. Metabolic syndrome was present in 10-14% of participants, substantially lower than found in the D:A:D study. However, in the D:A:D study metabolic syndrome was based on their own definitions to account for a large amount of missing data.

Table 1.2: Metabolic Consequences of HIV Infection and Antiretroviral Therapy

	Aetiology	Consequences	Current Prevalence and Treatment	Refs
Dys-lipidaemia	Traditional and HIV-related factors contribute, raised cytokines, particularly interferon-α, and down-regulation of PPAR-γ secondary to certain ARVs	Raised TGs, apo B, and VLDL-c. HDL may be suppressed or increased depending on disease state and ARVs. Plaque formation/ calcification, MIs result	Highly prevalent. Switch ARV therapy, statin and other pharmaceutical agents, lifestyle change	1,2
Lipo-dystrophy	Mitochondrial toxicity, cytokine and adipokine alterations, all secondary to certain ARVs	Lipoatrophy or hypertrophy of fat, association with cardiometabolic disease	Rare incidence, prevalence declining. Switch ARV therapy, fillers for lipoatrophy, progressive resistance exercise	3
Hepatic Steatosis	Traditional metabolic risk factors contribute. HIV is not independently associated	Compared to HIV-controls, fatty liver disease has increased disease severity in HIV+	Increasing prevalence correlated with obesity. Weight loss, tesamorelin therapy	4
Vitamin D deficiency	Vitamin D catabolism and inhibition of renal hydroxylation by certain ARVs; also inflammation	Early onset of osteopaenia and osteoporosis	Highly prevalent. Vitamin D replacement, safe sunlight exposure, switch ARV therapy	5
Hypo-gonadism	Hypothalamic-pituitary dysfunction, poor nutrition, wasting	Exacerbation of wasting, lethargy, impaired sexual function	Common, incidence declining. Testosterone replacement therapy	6
Lactic Acidosis	ARV-related mitochondrial toxicity disrupts ribonucleic acid metabolism, increasing lactate production	Hepatic steatosis impairs lactate clearance. Increased serum lactate can be asymptomatic; high levels are potentially fatal	Very rare. Switch ARV therapy, limited evidence base for treatment with nutritional agents including B vitamins and l-carnitine	7
Futile Metabolite Cycling	Cytokine disturbance and inflammation secondary to HIV	Raised triglycerides (TGs), decreased clearance of VLDL-c, resting energy expenditure higher	Rare. Introduction of ARV therapy	8
References: 1 - Christeff et al., 2002; 2 - (Christeff et al., 2002, Tripathi et al., 2013); 3 - (Weirzbicki et al., 2008); 4 – Stanley and Grinspoon, 2012; 5 - (Szep et al., 2011); 6- (Rochira et al., 2015); 7 - (Falco et al., 2002); 8 - McCutchan et al., 2012.				

Source: Review by A Duncan

1.3.3 Ageing with HIV

Ageing in PLWH forms a research focus in well-resourced countries investigating whether conditions associated with ageing are accentuated and/or accelerated in PLWH. These conditions include osteoporosis, cardiovascular disease, and importantly for research presented in this thesis, type 2 diabetes. Current opinion and evidence is summarised in Table 1.3 and particular issues regarding the relationship between ageing in HIV and T2D are discussed later in Section 1.3.4.

Table 1.3: The Prevalence and Aetiology of Conditions Associated with Ageing in HIV

	Aetiology	Accelerated or Accentuated?	Refs
Coronary Heart Disease	Dyslipidaemia, endothelial dysfunction and inflammation associated with both HIV and ARVs lead to deposition of atherosclerotic plaques	7 studies published 2002-12 show a doubled risk for myocardial infarction (MI) in HIV patients when controlling for known risk factors, but do not demonstrate an accelerated process. MI incidence in HIV declining, postulated as secondary to smoking cessation and use of ARVs with less toxicity	1,2
Osteoporosis	Vitamin D deficiency, inflammation, and potential ARV toxicity lead to loss of bone mineral density	Osteopaenia and osteoporosis are more common in HIV patients than in HIV negative controls, occurring at a younger age than expected, with a 22% higher lifetime fracture risk	3,4
Chronic Kidney Disease	Nephropathy caused directly by HIV, ARV toxicity, hypertension	Risk of end-stage kidney disease in HIV is 2.56 per 1000 patient years (PY) compared to 1.68 in HIV negative. Occurs 5.5 months earlier compared to controls	5
Cognitive Decline	Damage caused directly by HIV and inflammation	Further research needed and ongoing. Currently HIV-associated neurocognitive decline occurring in 30-50% of patients	6
Stroke	Inflammation, hypertension, cardiovascular disease	High incidence of hypertension among adults and children with HIV. Controlling for known factors, stroke incidence is 17% higher compared to HIV negative	7-9
Non-AIDS Defining Cancers (NADCs)	Inflammation, immunodeficiency, viral coinfections	NADC incidence is 4.65 per 1000 PYs in HIV compared to 2.24 in matched HIV-controls. Strong association with age	5
References: 1-2 (Grinspoon, 2015, Klein et al., 2015); 3-4 (Brown and Qaqish, 2006, Peters et al., 2013b); 5 - (Althoff et al., 2015); 6 - (Cohen et al., 2015); 7-9 (Chow et al., 2014, Sico et al., 2015, Chatterton-Kirchmeier et al., 2015).			

Source: Review by A Duncan

1.3.4 Morbidity and Mortality Associated with Metabolic Disease and Ageing

A comparison of data collected from commercial healthcare databases in the United States shows that there were higher rates of comorbidities among HIV patients in 2013 compared to 2003 (Schouten et al., 2014). Increases occurred in type 2 diabetes (12.7% vs. 8.3%), hypertension, hyperlipidaemia, cardiovascular disease, and renal impairment. Given these trends were observed among all age groups, the researchers suggested that age may not be the sole influence on comorbidity incidence. Older PLWH have a greater incidence of complications compared to HIV negative adults of similar age and are characterised by a frailty phenotype defined as a decrease in lean body mass, weight, physical strength, energy, and combined with decreased levels of physical activity (Althoff et al., 2014).

Dyslipidaemia is the most prevalent metabolic comorbid condition in HIV, present in 47% of a London cohort in 2005 (Aboud et al., 2010), 36% in a North American cohort in 2010-11 (Willig et al., 2015) and rising to 67% in a large study conducted in East Africa in 2010 (Armstrong et al., 2011). Among those without hepatitis co-infection, CVD accounts for 38% of mortality, measured in a large cohort in the USA (Wada et al., 2014). Although the associated risk for cardiovascular disease (CVD) and myocardial infarction (MI) is higher in HIV, mortality rates due to CVD have declined since 2001 due to improved care and lifestyle change (Hasse et al., 2011, Grinspoon, 2015).

Despite the increased morbidity described, there is emerging evidence that life expectancy in HIV may be higher than matched HIV negative controls in White males who regularly attend their HIV outpatient appointments. Investigators suggest this may be due to regular checks with HIV physicians facilitating early diagnosis and treatment of illnesses and conditions unrelated to HIV infection (Samji et al., 2013).

1.3.5 Body Composition, Weight Gain, and Obesity in HIV

Malnutrition associated with HIV infection, once highly prevalent, is now rare in PLWH treated with HIV medicines; weight gain and obesity are now highly prevalent (Yuh et al., 2015). Discussed in this section are concerns regarding obesity now being a major determinant of poor health in HIV.

Prior to the introduction of HAART treatment prevention of wasting of lean body mass (LBM) was a primary goal to reduce HIV-associated mortality. In a landmark study, investigators demonstrated a linear relationship between wasting of LBM and time before death (Kotler et al., 1989). In the modern HAART era although undernutrition is much less common (Table 1.4), treatment and reversal of weight loss and wasting remains a primary aim of medical nutritional therapy (Siddiqui et al., 2009, Mangili et al., 2006). Normalisation of BMI in those who are underweight is recommended in US clinical guidelines (Fields-Gardner et al., 2010) and by the European Society for Enteral and Parenteral Nutrition (ESPEN) (Ockenga et al., 2006).

The incidence of undernutrition in PLWH has declined and rates of obesity have increased in proportion with the numbers treated with HAART (Table 1.4). Cardiovascular disease, T2D and other conditions associated with obesity are now the main cause of morbidity and mortality in HIV in well-resourced countries, with rates likely to continue increasing secondary to ageing (High et al., 2012). Obesity in older PLWH is associated with frailty (Shah et al., 2012).

In a South London-based study of PLWH investigators have characterised how overweight and obesity has changed over time (McCormick et al., 2014). Those who were obese increased from 8.5% in 2001 to 28.0% in 2011-12. Female gender and Black African ethnicity were particularly associated with BMI. Among women of Black African origin, 81% were overweight or obese, compared to 49% of White men. Investigators explored possible explanations for such a high prevalence of overweight and obesity among Black African women. There appeared to be no significant correlation with ARVs or concomitant clinical factors. Black African women underestimated their weight, expressed less dissatisfaction with their body shape, and less awareness of increased cardiovascular risk. The authors acknowledged a limited ability to compare findings with the general population, concluding that high rates of obesity warrant intervention.

Table 1.4: Prevalence of Undernutrition, Overweight and Obesity in HIV

Cohort	Data Collected	Prevalence of Under-nutrition	Prevalence of Overweight and Obesity	Comments	Ref
2557 HIV+ and 730 HIV- women, USA	1994 and 2001	2% in HIV+ 2% in HIV-	61% HIV+ 60% HIV-	Underweight significantly associated with advanced HIV disease	1
1669 outpatients, USA	2003	9%	45%	Obesity most common in women and African Americans	2
681 outpatients, USA	2008	8%, declining to 4% after 2 years HAART	44%, after 2 years 64%	Those with a CD4<50 gained most weight	3
Hospitalised patients, Brazil	2009-2010	43%	Not reported	16% of those with undernutrition died	4
149 Female outpatients, South Africa	2011-2012	1% (CD4 ≥350) 11% (CD4 ≤200)	44% ARV naive 65% on ARVs 65% in HIV-	Undernutrition correlated with immunosuppression, obesity with ARVs	5
1,800 outpatients, USA	2010-2011	Not reported Mean BMI 27.2	Obesity: 24.7%	Obesity (BMI ≥30) reported only. Black women 49.0%, White men 14.9%.	6
40 outpatients aged 50 and over, USA	2011	Not reported	Frail: Mean BMI 31, non-frail: Mean BMI 26	Correlation between central obesity and frailty in older adults with HIV	7
4311 patients, USA	2000-2014	6%	30% overweight, 13% obese	Weight gain following initiation of HAART is associated with lower mortality for those not initially overweight	8
Up to 1166 HIV patients, UK	2001-2012	1% in 2011-12	Obese: 8.5% in 2001, 28.0% 2011-12	Highest overweight and obesity prevalence: Black African women	9
References: 1 - (Boodram et al., 2009); 2 - (Amorosa et al., 2005); 3 - (Tate et al., 2012); 4 - (Andrade et al., 2012); 5 - (Wrottesley et al., 2014) ; 6 - (Willig et al., 2015); 7 - (Shah et al., 2012); 8 - (Yuh et al., 2015); 9 - (McCormick et al., 2014).					

Source: Review by A Duncan

Weight gain following initiation of HAART is common (Lakey et al., 2013) and is known to be associated with subsequent development of dyslipidaemia (Grinspoon and Carr, 2005) and with later development of CVD and T2D. In the international Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort study (n=9,321), investigators reported on correlations between the development of either CVD or T2D and weight gain in the first year following

initiation of HAART (Achhra et al., 2015). For CVD the incidence ratio rate per unit gain in BMI in the first 12 months of ARV therapy categorised by pre-ART BMI was: underweight, 0.90; normal, 1.18; overweight, 0.87, and obese, 0.95. For T2D, the incidence ratio rate per unit gain in BMI was 1.11 regardless of pre-ART BMI. Investigators leading the North American Veterans Aging Cohort study reported findings after 5 years of following up 4,311 patients who experienced a modest median weight gain of 2.7kg during the first 12 months of HAART (Yuh et al., 2015). Both studies agree that weight gain following initiation of HAART appears to be strongly associated with subsequent development of T2D.

1.4 Type 2 Diabetes

1.4.1 Introduction

Type 2 diabetes mellitus is a metabolic condition characterised primarily by hyperglycaemia, resulting from inefficient insulin function. It is associated with considerable morbidity and mortality, and is more than three times more prevalent than all cancers combined (Diabetes UK, 2015). Prediabetes, commonly referred to as borderline diabetes, is also characterised by hyperglycaemia, with blood glucose levels above normal but below the threshold defining T2D (see Table 1.6).

Diabetes is now recognised as a global pandemic with a diabetes-related mortality rate for 2015 of 1.6 million and a predicted 2040 prevalence of 642 million (International Diabetes Federation, 2015, Whiting et al., 2011). Type 2 diabetes is associated with obesity and age, and its increasing prevalence is reflected in 2015 data from the UK (International Diabetes Federation, 2015): in the UK there are an estimated 3 million people with T2D. The annual NHS diabetes-related expenditure is £5,808 for each person with T2D, with diabetes accounting for 15% of the UK's entire health budget (Hex et al., 2012).

1.4.2 Prediabetes and Type 2 Diabetes: Aetiology and Pathophysiology

Development of both prediabetes and T2D takes place over an extended period of months and years. Their aetiology comprises three principal components: heritability with polygenic components; a strong association with excess body fat; and gene-environment interactions. Prediabetes increases lifetime risk of T2D by 70-90% (Narayan et al., 2003) although this risk can be mitigated through diabetes prevention measures discussed in section 1.4.3. Prediabetes and T2D are similar in aetiology and pathophysiology. They are characterised by chronic surplus energy balance, resulting in fat deposition both within adipocytes and ectopically, typically within and between hepatocytes, pericardially, and in muscle tissue (American Diabetes Association, 2014). This excess fat deposition is associated with increasing levels of inflammatory cytokines and the development of insulin resistance. Development of prediabetes and T2D can also occur in leaner individuals, here clearly associated with factors other than obesity such as genetic polymorphisms, medication or hepatic disease (Hu, 2011).

Progression from prediabetes to T2D is not inevitable; treatment of obesity can reduce risk. For those with isolated IGT or combined IFG and IGT the lifetime risk of developing T2D approaches 90% (Narayan et al., 2003). Annual conversion rates from prediabetes to T2D vary from 4% to 19% depending on combination of IFG and IGT (de Vegt et al., 2001, Li et al., 2003).

Resistance to the actions of insulin and resulting post-prandial hyperglycaemia initially leads to increased insulin release. This hyperinsulinaemic response can continue asymptomatically until impaired pancreatic β–cell function and eventually β–cell failure leads to insufficient insulin release and chronic hyperglycaemia, necessitating injected insulin therapy (Gerich, 2002).

A normal metabolic response to food consumption, digestion and increasing blood glucose levels is characterised by a rapid first-phase insulin secretion, usually within 10 minutes, followed by a more durable second phase, characterised by a peak or plateau of insulin between 90 and 120 minutes (Del Prato et al., 2002). Two intestinal insulin-stimulating hormones, the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are important (Vilsboll and Holst, 2004). As plasma glucose increases, glucose transporters on the surface of pancreatic β-cells allow a greater influx of glucose. This results in an increased adenosine triphosphate to adenosine diphosphate ratio, closing channels allowing potassium to leave the β-cell. Membrane depolarisation then occurs followed by opening of calcium channels, with the resulting calcium influx triggering exocytosis

of awaiting insulin granules. The incretin hormones are thought to amplify the insulin secretion pathway leading to an increase in the number of granules. The incretin effect can become diminished or absent in prediabetes and T2D. As well as stimulating insulin release, GLP-1 suppresses glucagon production, limiting gluconeogenesis in the liver (Cefalu, 2010). Insufficient GLP-1 can explain impaired fasting glucose prevalent in T2D.

Epidemiological studies suggest that IFG and IGT only partially overlap (Abdul-Ghani et al., 2006), with IGT characterised primarily by muscle and not hepatic insulin resistance, whereas in IFG hepatic insulin resistance with relatively normal muscle insulin sensitivity occur. Both IFG and IGT can be characterized by a reduction in first-phase insulin release although mechanisms appear to vary by ethnicity (Aoyama-Sasabe et al., 2016). Individuals with IGT also have impaired second-phase insulin secretion (Abdul-Ghani et al., 2006).

The development of prediabetes and T2D is associated with a range of modifiable and fixed factors as listed in Table 1.5. Investigators have demonstrated that despite the diversity of factors T2D is largely driven by obesity, potentially explaining the synchronicity between the increasing global prevalence of both diabetes and obesity (Hu, 2011).

Table 1.5: Factors Associated with Risk of Development of Prediabetes and Type 2 Diabetes

Fixed	**Modifiable**
Age	Obesity: body mass index and waist
Non-White Ethnicity	Sedentary Lifestyle
First degree relative with diabetes	Use of medications associated with dysglycaemia
Gestational diabetes	Raised LDL-cholesterol
Polycystic Ovary Syndrome	Raised triglycerides
Pro-inflammatory conditions	Chronic dietary energy excess
Menopause	High sugar intake
Socioeconomic status	Low fibre intake
Historic use of medications associated with dysglycaemia	

Source: (Muhlenbruch et al., 2013)

Diabetes is diagnosed using WHO criteria (Table 1.6). Prediabetes encompasses both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) as outlined in Table 1.6. The clinical blood test definition of diabetes is universal, whereas the threshold for diagnosis of prediabetes differs in the United States (American Diabetes Association, 2014).

T2D increases the risk of CVD and stroke, as well as increasing the risk of admission to hospital (American Diabetes Association, 2014). In the UK T2D is a leading cause of blindness, kidney failure and amputation, resulting from chronic hyperglycaemia (Diabetes UK, 2015).

Table 1.6: Clinical Definitions of and Screening for Prediabetes and Type 2 Diabetes

	HbA1C Units (%)	Fasting Glucose Test	Random Glucose Test (Non-fasting)	OGTT 2-hour glucose
Normal Glycaemia	20-41 (4.0-5.9%)	≤5.9 mmol/l	≤7.7 mmol/l	≤7.7 mmol/l
Prediabetes (WHO definition)	42-48 (6.0-6.5%)	6.0-6.9 mmol/l (IFG)	7.8-11.0 mmol/l (IGT)	7.8-11.0 mmol/l (IGT)
Prediabetes (ADA definition)	42-48 (6.0-6.5%)	5.6-6.9 mmol/l (IFG)	7.8-11.0 mmol/l (IGT)	7.8-11.0 mmol/l (IGT)
Type 2 Diabetes	≥49 (≥6.6%)	≥7.0 mmol/l	≥11.1 mmol/l	≥11.1 mmol/l
NOTES: WHO clinical definitions are used globally apart from the USA where ADA definitions are used. HbA1C – glycosylated haemoglobin OGTT – Oral Glucose Tolerance Test				

Source: (International Diabetes Federation, 2015)

1.4.3 Lifestyle Prevention of Type 2 Diabetes

Risk of type 2 diabetes can be mitigated by treatment with medications such as metformin and by reduction in insulin resistance secondary to dietary change, exercise or weight loss achieved through lifestyle modification (Muhlenbruch et al., 2013). A series of cross-sectional studies have suggested there may be an association between certain components of the diet and risk for development of T2D. My review of these studies is summarised in Table 1.7.

There is strong evidence from major randomised controlled trials (RCTs) that diet and physical activity interventions can prevent or delay progression to T2D in those at high risk across different ethnic backgrounds (Knowler et al., 2002, Pan et al., 1997, Ramachandran et al., 2006, Tuomilehto et al., 2001) (see Table 1.8). The risk of diabetes is reduced by between 28% and 59% after implementation of lifestyle change (Walker et al., 2010) There is also evidence of prolonged benefit, with investigators leading three of the major trials reporting a lower incidence of diabetes at 7-20 years follow-up beyond the planned intervention period

(Diabetes Prevention Program Research et al., 2009, Li et al., 2008, Lindstrom et al., 2006). Common to the lifestyle prevention trials listed in 1.8 are goals to achieve moderate weight loss, change in dietary intake and increased physical activity. However, apart from reducing fat intake dietary goals were not identical across all four trials.

The most significant factor for diabetes prevention is weight loss. Each 1.0 kg reduction is associated with a 16% risk reduction (Hamman et al., 2006). How to achieve this weight loss varies across trials although the four diabetes prevention RCTs used broadly similar healthy eating goals as promoted by global diabetes organisations (American Diabetes et al., 2008), (Ha and Lean, 1998), (Connor et al., 2003). Alternative dietary methods can also be effective. The Mediterranean Diet (Martinez-Gonzalez et al., 2008), carbohydrate restriction (Hession et al., 2009), the Dietary Approaches to Stop Hypertension (DASH) diet (Liese et al., 2009) and meal replacement (Noakes et al., 2004) approaches have all shown benefit in reducing T2D risk. This flexibility in dietary approaches is of great clinical utility (Walker et al., 2010).

The Predimed trial (Salas-Salvadó et al., 2011) demonstrated that the Mediterranean diet reduced progression to T2D by 50% compared to a low-fat diet. Investigators randomised participants to a non-calorie restricted diet (Mediterranean plus either olive oil or mixed nuts, or a low fat diet). Over 4 years, participants lost a mean 0.6 kg. This trial demonstrated that it is possible to prevent or delay T2D through dietary change without significant weight loss.

Both the Predimed trial and the Finnish DPP demonstrated that number of diet and exercise goals achieved is associated with reducing risk of development of T2D (Schwarz et al., 2012). In Predimed, for example, 6.3% of participants achieving at least half of the number of goals set progressed to T2D, compared to 15.0% of those achieving fewer than half.

In terms of the individual contribution of components of lifestyle interventions for diabetes prevention, findings from the DaQing trial suggest that there was no significant difference in progression to diabetes in those allocated either diet or exercise alone, or both together (Pan et al., 1997). Meta analyses have attempted to look at this issue, drawing together results from the four major RCTs combined with smaller trials, and a review supports the DaQing trial findings that there is no significant difference between isolated diet or physical activity approaches, or both together (Gillies et al., 2007), although there is evidence that in the absence of weight loss, increased levels of physical activity can reduce T2D incidence by 44% (Hamman et al., 2006).

Table 1.7: Dietary Factors Associated with Type 2 Diabetes Risk

Dietary Factor	Description	Effect on Risk of T2D	Refs	Research Quality
Whole grains	3 portions wholegrains per day	↓ RR=0.68	1-3	**1b** Meta-analysis of 16 studies
Dietary Fibre	High fibre intake	↓	4,5	**2a** Meta-analysis of 8 studies
Glycaemic Index	Diets of low glycaemic index/load	↓	6,7	**1b** Meta-analysis of 21 studies
Fruit and Vegetables	High intakes of dark yellow and leafy green vegetables; higher total vegetable intake; greater variety of fruit and vegetables	↓	8,9,24	**2a** Meta-analysis of 10 studies
Dairy foods	High intakes of low fat dairy products	↓	10,11	**2a** Meta-analysis of 14 studies
Coffee	High intake – dose reponse up to 6 cups per day, but more research needed	↓	12,13	**2b** Meta-analysis of 28 studies
Alcohol	Moderate intake – peak risk reduction 10-14 g alcohol /day, but may be confined to women and non-Asian ethnicities	↓	14,15	**2b** Meta-analysis of 17 studies
Potatoes	High intake, including fried potatoes	↑	16	**3** 1 study, women only
Fats	High intake of total and saturated fat, although full-fat dairy may reduce risk. Further research required	↑	17,18	**3** Conflicting evidence
Sugar	High intake of sugar-sweetened drinks and fruit juice	↑	19	**2a** Meta-analysis of 17 studies
Meat	Higher red meat intake. RR = 1.19 and 1.51 for 100g unprocessed and 50g processed red meat/day	↑	20-23	**2b** Meta-analysis of 3 studies

References: 1 - (Fung et al., 2002); 2 - (Murtaugh et al., 2003); 3 - (Aune et al., 2013); 4 - (Barclay et al., 2008); 5 - (InterAct, 2015); 6 - (Schulze et al., 2004); 7 - (Greenwood et al., 2013); 8 - (Liu et al., 2004); 9 - (Li et al., 2014); 10 - (Choi et al., 2005); 11 - (Gao et al., 2013); 12 - (van Dam et al., 2006); 13 - (Ding et al., 2014); 14 - (Wannamethee et al., 2003); 15 - (Knott et al., 2015); 16 - (Halton et al., 2006); 17 - (Riserus et al., 2009); 18 - (Ericson et al., 2015); 19 - (Imamura et al., 2015); 20 - (Fung et al., 2004); 21 - (van Dam et al., 2002); 22 - (Pan et al., 2011); 23 - (Kurotani et al., 2013); 24 – (Muraki et al., 2013).

Source: Review by A Duncan

Table 1.8: Diabetes Prevention Lifestyle Intervention Randomised Controlled Trials.

Trial and Cohort	Design	Outcomes	Reference
The DaQing IGT and Diabetes Study, China. n=577 with IGT, variable BMI, 6-year follow up	4 arms: (1) dietary change (increase fruit, vegetables and fibre, reduce alcohol, energy restriction) (2) increased PA (brisk walking 20 minutes per day) (3) both (4) standard care	Conversion to T2D in control arm: 68%. Risk reduction (RR) for intervention arms: Diet – 48% Exercise – 41% Both – 46%	(Pan et al., 1997)
Diabetes Prevention Programme (DPP), USA. n=3234 with IGT, mean 2.8 year follow up	4 arms: (1) Intervention - energy deficit of >500 kcal/day to achieve 7% weight reduction in 6 months, fat <25% total energy intake, 150 mins PA/week (2) Metformin (3) Troglitazone (withdrawn due to toxicity concerns) (4) placebo	Control group diabetes conversion rate: 11.0% per year. Lifestyle intervention arm RR 58%; metformin arm RR 31%	(Knowler et al., 2002)
Finnish Diabetes Prevention Study (DPS) n=522 with IGT and mean BMI 31, mean 3.2 year follow up	2 arms: (1) intervention - at least 5% weight loss, fat <30% total energy intake, fibre >15g/1000 kcal, 4 hours PA/week. (2) standard care	≥5% weight loss – RR 74%; ≥4 hours PA/week – RR 80%. 3 year follow-up post intervention: RR 43%	(Tuomilehto et al., 2001)
Indian Diabetes Prevention Study n=531, with IGT, mean BMI 25.8, mean 2.5 year follow up	4 arms: (1) Intervention - Avoid sugars, fat intake <20 g/day, increase fibre, vegetables and fruits, 30 min brisk walking/day (2) Metformin (3) both (4) placebo	Lifestyle intervention RR 28.5%, metformin 26.4%, combined 28.2%	(Ramachandran et al., 2006)
Notes: IGT: Impaired Glucose Tolerance; PA: Physical Activity; RR: Risk Reduction			

Source: Review by A Duncan

Work is ongoing to translate diabetes prevention RCTs into routine clinical practice. A systematic review and meta-analysis found a greater pooled weight loss observed for those studies including a larger number of evidence-based goals (Dunkley et al., 2014, Public Health England, 2015c, NICE, 2012). Studies restricting recruitment to participants with an initial BMI ≥25kgm^2 lost significantly more pooled weight than studies with open recruitment. A greater intervention effect was observed with contacts that were more frequent, of longer duration and evenly spread across the intervention period.

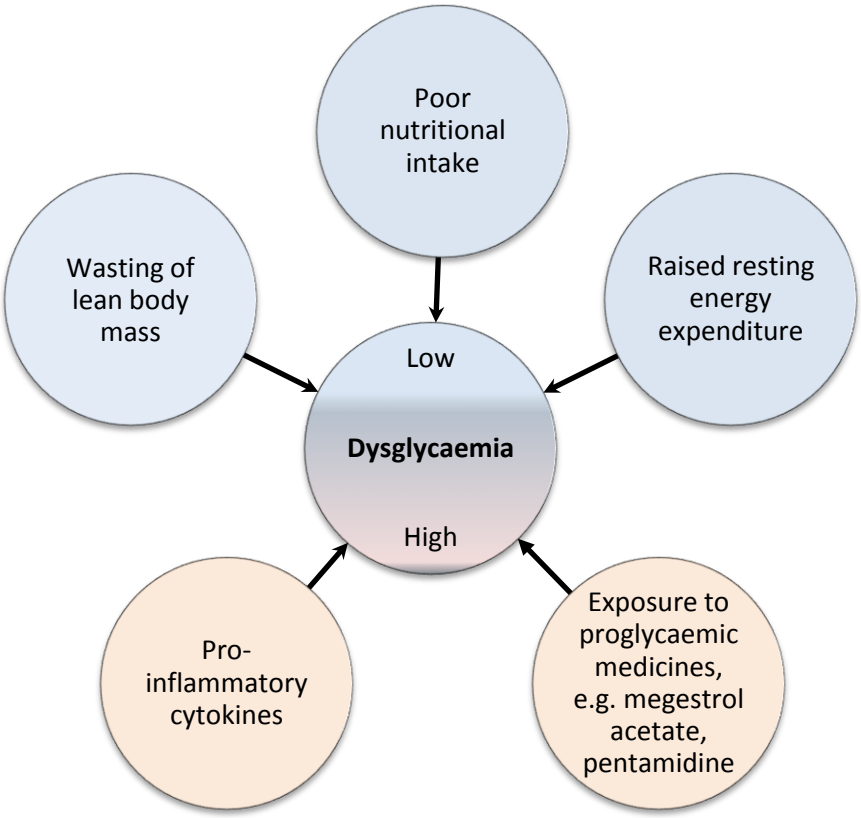
1.5 HIV and Type 2 Diabetes Comorbidity

This section presents a review of the aetiology and prevalence of type 2 diabetes in HIV. Non-lifestyle change interventions are reviewed. The clinical implications and current care guidelines for people living with both conditions are discussed.

1.5.1 Dysglycaemia Prior to Treatment with HAART

Prior to the development of HAART, hypoglycaemia was observed in patients experiencing AIDS-related weight loss and this was thought to be associated with poor nutritional status, wasting of LBM, and raised resting energy expenditure (Stein et al., 1990). In a study performed in the earlier years of the HIV epidemic, investigators using the hyperinsulinaemic-euglycaemic clamp method measured glucose and insulin dynamics in healthy, stable HIV positive people and compared them to HIV negative controls (Hommes et al., 1991). They found that, unlike with other infectious disease, in HIV insulin sensitivity and glucose clearance were both increased. However, in those unwell with HIV, insulin resistance characterised by hyperinsulinaemia was reported to be characteristic of the host cell response to infection by HIV (Hadigan et al., 1999). Researchers postulated that this was due to release of pro-inflammatory cytokines, particularly TNF-α, by peripheral leucocytes (Limone, 2003). Prior to the use of HAART, recombinant human growth hormone and the appetite stimulant megestrol acetate were used to treat AIDS-related wasting, and pentamidine was used to treat and prevent Pneumocystis pneumonia, all of which have a strong potential to disturb glucose homoeostasis (Hadigan et al., 1999). Most iatrogenic hyperglycaemia occurs due to drug-induced insulin resistance and is potentially reversible although certain medications including pentamidine cause more permanent β-cell dysfunction or cytosis. Researchers demonstrated that in those patients with serum glucose >6.9 mmol/l, half of cases could be attributed to drug-induced hyperglycaemia, specifically megestrol acetate in that cohort (Kilby and Tabereaux, 1998).

Figure 1: Mechanisms Associated with the Pre-HAART Aetiology of Dysglycaemia in HIV



Source: A Duncan

1.5.2 Prevalence and Phenotype of Type 2 Diabetes in HIV in the HAART Era

In a review of 6 studies, Hadigan and Kattakuzhy suggest that PLWH treated with ARVs are up to four times more likely to have T2D compared to negative controls matched for age, ethnicity and BMI although prevalence depends on the cohort studied (Hadigan and Kattakuzhy, 2014). They describe prospective observational and cross-sectional studies investigating incidence, prevalence and factors associated with T2D in HIV in cohorts including participants based in the United States, Brazil, Denmark and France. However, there has been no published research regarding the phenotype of T2D in HIV in the UK, and no work in progress from searches of clinical trials registers. Investigators suggest that in PLWH, T2D may be driven by a combination of HIV infection itself, ARVs and traditional factors such as age and

central obesity. These and other studies are included in my review of published literature regarding T2D in HIV presented in Table 1.9.

The reported prevalence of T2D varies from 2.6% to 14% according to the HIV cohort studied. The lowest prevalence was observed in an ARV-naïve population (El-Sadr et al., 2005) and the highest in a treatment-experienced cohort (Brown et al., 2005). Investigators in these studies compared their HIV T2D prevalence rates to T2D in the local general population and found prevalence ratio rates range from 0.6 to 5.0 times respectively. Incidence of T2D also varies according to cohort studied. Three studies suggest that whereas in the early years of HAART treatment (1996-98) there was a higher risk of developing T2D, more recently (1999-2010) there is no significant difference in T2D incidence between HIV negative and positive individuals (Rasmussen et al., 2012, Tien et al., 2007, Polsky et al., 2011). The highest relative rate of 4.1 was observed in a treatment-experienced cohort from the USA (Brown et al., 2005).

Among treated HIV positive adults, the risk for T2D appears to vary according to several factors. These have been partially characterised in several cohorts but not in the UK, and include female gender, BMI, age, Black (African American) ethnicity, CD4 nadir, and a history of treatment with certain ARVs (Samaras, 2012). Other factors significantly associated with dysglycaemia in HIV include lipodystrophy where patients are more than twice as likely to develop T2D (Capeau et al., 2012).

An increased risk for T2D has been demonstrated across a range of HIV cohorts including vertically transmitted children and young adults where exposure to ARVs associated with dysglycaemia may have been widespread (Aldrovandi et al., 2009), and in pregnancy (Gonzalez-Tome et al., 2008). However, among newly HIV-diagnosed individuals there appears to be no added risk for T2D (Shen et al., 2013).

Table 1.9: Review of Cohort Studies of Dysglycaemia in HIV

Citation	Data Collection	Description of Study	Cohort	Principal Findings	Research Quality
(Kilby and Tabereaux, 1998)	1988-1995, USA	Cross-sectional study, pre HAART era. Prevalence of T2D and drug-induced hyperglycaemia	n=1392, mean age 42, 80% male	Prevalence of glycaemia >6.9 mmol/l was 1.8%. Of these 25 participants, 10 were prescribed megestrol acetate	3
(Tripathi et al., 2013)	1994-2011, USA	Prospective observational cohort study investigating incidence of T2D in HIV+ patients compared to matched HIV-	n=6816, mean age 39, 57% male, 71% Black, 80% on HAART, 10% BMI ≥30	Lower prevalence and incidence of T2D in HIV vs. controls (mean follow-up 5.8 years): 7% and 9% respectively initial prevalence, incidence 1.14 and 1.36 per 100 patient years.	2b
(Justman et al., 2003)	1995-1998, USA	Prospective observational study investigating incidence of T2D in a cohort of HIV+ women compared to matched HIV-	n=1435 HIV+, 385 HIV-; mean age 37, 100% female, 55% Black, 26% Hispanic, mean BMI 25.5 HIV+, 26.4 HIV-	Incidence of T2D in HIV+ was 2.8 per 100 patient years for those on PIs, and 1.2 for both ARV naïve and those prescribed non-PI HAART. Incidence of T2D for HIV- was 1.4 per 100 patient years. Note higher mean BMI in HIV-	2b
(Rasmussen et al., 2012)	1996-2010, Denmark	Prospective observational study investigating incidence of T2D in a national cohort of HIV+ patients compared to matched HIV-	n=3540, mean age 38.7, 84% male, 2.5% non-White 18% overweight or obese	Initial prevalence of T2D 3%. Mean follow-up 8 years: incidence 0.37 per 100 patient years for HIV+, 0.39 for HIV-. RR in HIV was 2.83 prior to HAART years (1996-1999), and 0.90 since 1999	2b
(Capeau et al., 2012)	France 1997-2009	Prospective observational study investigating incidence of T2D in a national cohort of HIV+ patients. Mean follow-up 9.6 years	n=1046, mean age 37, 79% male, 10% Black, mean BMI 22.1, 100% on HAART	Prevalence 10.6%, incidence 1.41 per 100 patient years. Incidence peaked in 1999, declined after. Hazard ratios: >50 years 3.6; BMI>30 2.9; waist: hip ratio >0.97 males >0.92 females 3.9; lipoatrophy 2.1	2b
(El-Sadr et al., 2005)	1999-2002, USA	Cross-sectional study: T2D prevalence in ARV-naïve patients	n=419, 79% male, mean age 48, mean BMI 24.2	Prevalence of T2D 2.6%	3

Citation	Data Collection	Description of Study	Cohort	Principal Findings	Research Quality
(Brown et al., 2005)	1999-2003, USA	Multicentre prospective cohort study investigating prevalence and incidence of T2D in HIV+ compared to HIV-	n=568, 100% male, mean age 46	Prevalence of T2D 7% in naïve to ARVs, 14% on treatment. Incident T2D 4.7 per 100 person-years in HIV+ compared to 1.4 in HIV- (relative rate 4.1). Highly correlated with lipodystrophy	2b
(Saves et al., 2002)	1999, France	Cross-sectional study: phenotype of lipodystrophy and other metabolic complications	n=614, 80% male, mean age not stated but 63% >34 years	5.7% had T2D, all of whom were prescribed PIs, and the majority also prescribed AZT, ddI or d4T	3
(De Wit et al., 2008)	1999-2005, Europe, US, Australia, Argentina	Incidence of new-onset diabetes in large international D:A:D prospective observational study	n=33,389, mean age 38, male 74%, mean BMI 23.0	2.8% had T2D at entry; incidence rate 0.57 per 100 patient years and associated with cumulative ARV exposure, d4T, AZT and ddI, lipids, and lipodystrophy	2b
(Smith et al., 2014)	1999-2005, Europe, US, Australia, Argentina	Mortality data from the very large international D:A:D prospective observational study. Data analysed in 2013	N=49,731, mean age 46, mean BMI 23.8	2.8% had T2D at entry; 2006 – 3.1%; 2011 – 4.6%. Note: Relatively low BMI cohort. Mortality for those with T2D was 19.6% - mean overall mortality of 7.9%	2b
(Gonzalez-Tome et al., 2008)	2000-2003, Spain	Prospective cohort study investigating gestational diabetes in HIV+ women without T2D	N=669, mean age 31.	7% had gestational diabetes, independently associated with age and exposure to PIs. Compares with 4.5% rate in general population	2b
(Tien et al., 2007)	2000-2006, USA	Prospective cohort study investigating incidence of T2D in HIV+ women (n=1524) compared to matched HIV- (n=564)	Mean age 39, 100% female, 56% Black, 28% Hispanic, mean BMI 26.8	T2D incidence per 100 patient years: HIV- 2.0, HIV+ naïve to ARVs 1.5, protease inhibitor-containing HAART 2.5, non-PI HAART 2.9	2b
(Ledergerber et al., 2007)	2000-2006, Switzerland	Retrospective cohort study investigating incidence of T2D	n=6513, mean age 38, 69% male, 84.5% White, 73% on HAART, mean BMI 22.5	Mean follow-up 6 years. Initial prevalence 1.9%, incidence 0.44 per 100 patient years. RR for: males 2.5, >60 years 4.3, Black participants 2.1, Asians 4.9, obesity 4.7	3

Citation	Data Collection	Description of Study	Cohort	Principal Findings	Research Quality
(Polsky et al., 2011)	2002-2005, USA	Prospective cohort study investigating incident dysglycaemia in older adults with or at risk of HIV	n=222 (HIV+), 47% male, mean age 50, mean follow-up 18.6 months	Overweight 37%, obese 24%. Initial prevalence – prediabetes 29%, T2D 5%. Incident prediabetes 19%, T2D 5%	2b
(Aldrovandi et al., 2009)	2004-2005, USA	Cross-sectional study comparing lipids and glycaemia in HIV+ and HIV- young people aged 7-24	n=240 HIV+, 146 HIV-. HIV+: mean age 12.6	HOMA significantly higher in HIV+: 2.3 vs 1.5; all lipid fractions significantly different in HIV+	3
(Galli et al., 2012)	2008, Italy	Cross-sectional study comparing T2D risk in HIV+ and HIV-	n=4249 HIV+, 9148 HIV-. HIV+: mean age 46, 76% male, mean BMI 23.2	Prevalence of T2D in HIV+ 4.1%, 2.5% in HIV-, associated with age, BMI, hypertension, CD4 nadir, triglycerides, duration of HIV infection	3
(Calza et al., 2011)	2009, Italy	Cross-sectional study comparing lipids and glycaemia in HIV+, no HIV- comparison	n=755. Mean age with T2D 48, without T2D 37. 66% male	Prevalence of T2D 4.5%. Associated with age, BMI, treatment with HAART, lipodystrophy, and Hepatitis C	3
(Srivanich et al., 2010)	2009, Thailand	Cross-sectional study comparing risk for prediabetes in HIV+, no HIV- comparison	n=148, mean age 42, 65% male, 92% on HAART	Prediabetes prevalence was 27.5% associated with BMI (OR per 5kg weight gain 1.24), compared to general Thai population 5%	3
(Shen et al., 2013)	2009-2010, China	Cross-sectional study comparing risk for prediabetes and T2D in newly diagnosed HIV+ not yet on HAART, no HIV- comparison	n=2006, mean age 40, 76% male	9.5% had IFG, 10.5% had T2D. Age and lower CD4 were associated with T2D. Prediabetes and T2D in China have been reported as 9.7% and 11.6% respectively in the general population	3

Research Quality: 1 – Randomised Controlled Trial; 2a – Intervention without randomisation; 2b – Prospective Cohort Study; 3 – Cross-sectional study.
Abbreviations: AZT – zidovudine; ARV – antiretroviral; BMI – Body Mass Index; D:A:D - Data Collection on Adverse Events of Anti-HIV Drugs Study; d4T – stavudine; ddI – didanosine; HOMA – Homoeostatic Model of Assessment; HAART – Highly Active Antiretroviral Therapy; IFG - Impaired Fasting Glucose; OR – Odds Ratio; PI – Protease Inhibitor; RR – Relative Risk; T2D – Type 2 Diabetes.

Source: Review by A Duncan

1.5.3 The Aetiology of Dysglycaemia in HIV

The aetiology of dysglycaemia in HIV is complex, multifactorial, and not fully understood. Altered glucose homoeostasis in PLWH appears to be mediated by changes in adipocyte function, peripheral glucose disposal, hepatic insulin resistance and impaired β-cell insulin secretion (Hruz, 2011). In this section I have presented a summary of factors thought to contribute to dysglycaemia in HIV, including the direct effect of ARVs, gene-environment interactions, inflammation, leptin, vitamin D deficiency, and hepatic impairment.

The protease inhibitor (PI) class of ARVs, and in particular Indinavir and Ritonavir, may have a number of detrimental effects on metabolic health. Both have been shown to both increase insulin resistance through interference with glucose transport type 4 (GLUT-4)-mediated transport (Walli et al., 1998, Hadigan and Kattakuzhy, 2014, Loonam et al., 2016). Most protease inhibitors developed more recently are believed not to have this effect (Hruz, 2011). Ritonavir in particular has been shown to interfere with potassium signalling within β-cells impairing insulin release (Neye et al., 2006). Ritonavir in its most commonly-used lower boosting dose is not associated with insulin resistance (Taylor et al., 2010). Indinavir and to a lesser extent ritonavir impair the ability of insulin to suppress endogenous hepatic gluconeogenesis (Lee et al., 2009). PIs may also induce β-cell apoptosis (Zhang et al., 2009).

Those nucleoside reverse transcriptase inhibitors (NRTIs) associated with the development of lipodystrophy most likely induce insulin resistance through mitochondrial toxicity and are now rarely used (Samaras, 2012). In the Women's Interagency HIV Study, duration of exposure to the NRTI class drugs, especially stavudine, was found to be most closely related to insulin resistance (Tien et al., 2008). In the large international D:A:D cohort (De Wit et al., 2008), treatment with stavudine, zidovudine or didanosine all independently contributed risk to the development of T2D. In two other large prospective studies (Capeau et al., 2012, Brown et al., 2005), stavudine and indinavir were associated with insulin resistance and hyperinsulinaemia.

Insulin resistance in HIV appears to be associated with a combination of reduced peripheral uptake of glucose and impaired hepatic clearance of glucose (Haugaard et al., 2005). This effect has been observed in children vertically infected with HIV and on HAART, where only 1 out of 249 had IFG, but 7% had measured insulin resistance (Hazra et al., 2013).

As in the general population genetic factors appear to contribute in the development of diabetes in HIV. In a Swiss study comparing HIV positive and HIV negative participants, four polymorphisms were associated with T2D in HIV positive participants, estimated to contribute 14% of the variability in T2D risk (Rotger et al., 2010).

HIV-associated inflammation is thought to upregulate chemokines involved in insulin regulation (Hruz, 2011). In a US-based study higher levels of markers of TNF-α activation were significantly associated with the development of T2D after the first year of HAART (Brown et al., 2010). Increased levels of reactive oxygen species associated with HIV-related inflammation are thought to interrupt early insulin signalling pathways (Hruz, 2011). Increased microbial translocation across the gut which has been found to be higher in HIV patients compared to HIV negative controls can exacerbate inflammation and has been correlated with insulin resistance (Pedersen et al., 2013).

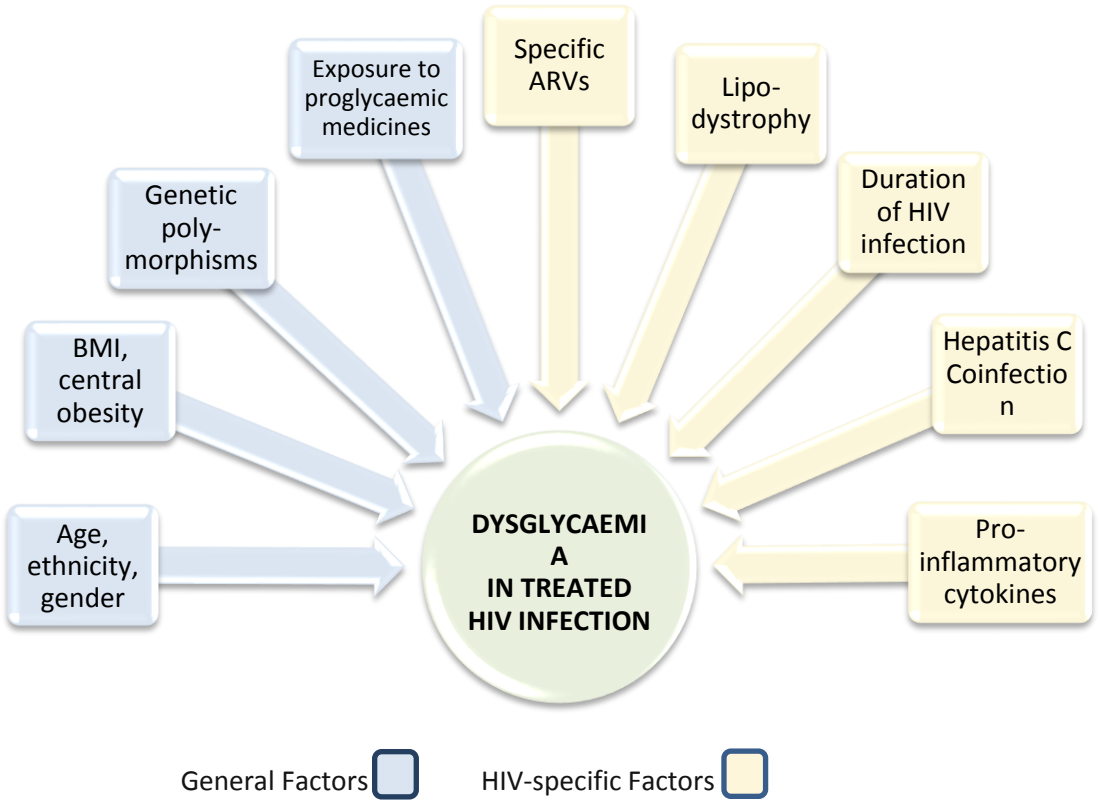
Reduced leptin levels have been associated with both insulin resistance and lipodystrophy in HIV patients (Deloumeaux et al., 2011, Veloso et al., 2012).

Vitamin D insufficiency, highly prevalent in HIV infection, was associated with both impaired β-cell response and insulin resistance in HIV positive participants without diabetes (Moreno-Perez et al., 2013). Supplementation with vitamin D increased insulin resistance at 24 weeks, although levels returned to baseline after 48 weeks (van den Bout-van den Beukel et al., 2008).

In a recent pilot study, correction of glutathione deficiency using cysteine and glycine supplementation demonstrated improved insulin sensitivity in older HIV positive patients (Nguyen et al., 2014).

Finally, investigators leading six studies have reported a strong signal for higher prevalence of T2D among hepatitis C (HCV) co-infected individuals (Howard et al., 2010, Calza et al., 2011, Berenguer et al., 2012, Bhagani, 2009, Butt et al., 2004, Capeau et al., 2012, Jain et al., 2007) compared to those with HIV or HCV alone. This added risk appears be mediated by non-alcoholic hepatic steatosis and liver fibrosis, both exacerbating insulin resistance. Hepatic lipid content in HIV positive participants irrespective of hepatitis status is correlated with degree of insulin resistance (He et al., 2008).

Figure 2: Factors Involved in the Aetiology of Dysglycaemia in Treated HIV Infection.



Source: A Duncan

1.5.4 Non-lifestyle Interventions for Insulin Resistance in HIV

There have been few medical or nutraceutical interventions for insulin resistance (IR) in HIV. In a pilot (n=9) trial of methionyl human leptin (metreleptin) in combination with pioglitazone in HIV patients with lipoatrophy, investigators demonstrated improved postprandial glycaemia and insulin sensitivity and a 15% reduction in central fat mass, but no effect on lipids or triglycerides (Magkos et al., 2011).

Two nutritional approaches to treating IR in PLWH have been investigated. Chromium supplements have been piloted (Feiner et al., 2008) and subsequently used in two randomised placebo-controlled trials at 400µg/day for 16 weeks (Aghdassi et al., 2010) and 1000µg/day for 8 weeks, with conflicting results reported (Stein SA, 2013).

Spirulina and soya bean supplements have been piloted in a small study that recruited participants in the Cameroons (Marcel et al., 2011). Drop-out rates were significantly different between the two arms, weakening claims that spirulina confers a greater chance of improving insulin sensitivity compared to soy.

1.5.5 Clinical Implications of HIV and Type 2 Diabetes Comorbidity

HbA1C in HIV Patients:

The screening and management of prediabetes and T2D in HIV present distinct challenges. Among HIV positive patients HbA1c is insensitive, although highly specific, for diagnosing diabetes. However, specific ARVs have a variable influence on the relationship between HbA1c and fasting glucose (Eckhardt et al., 2012). Treatment with ARVs can result in underestimation of glycated haemoglobin by up to 0.5 percentage units (4.5 mmol/mol) (Slama et al., 2014, Kim et al., 2009). The use of HbA1c in conjunction with a fasting glucose measurement or preferably an oral glucose tolerance test has been proposed to be the most reliable method for diabetes screening in HIV (Hadigan and Kattakuzhy, 2014).

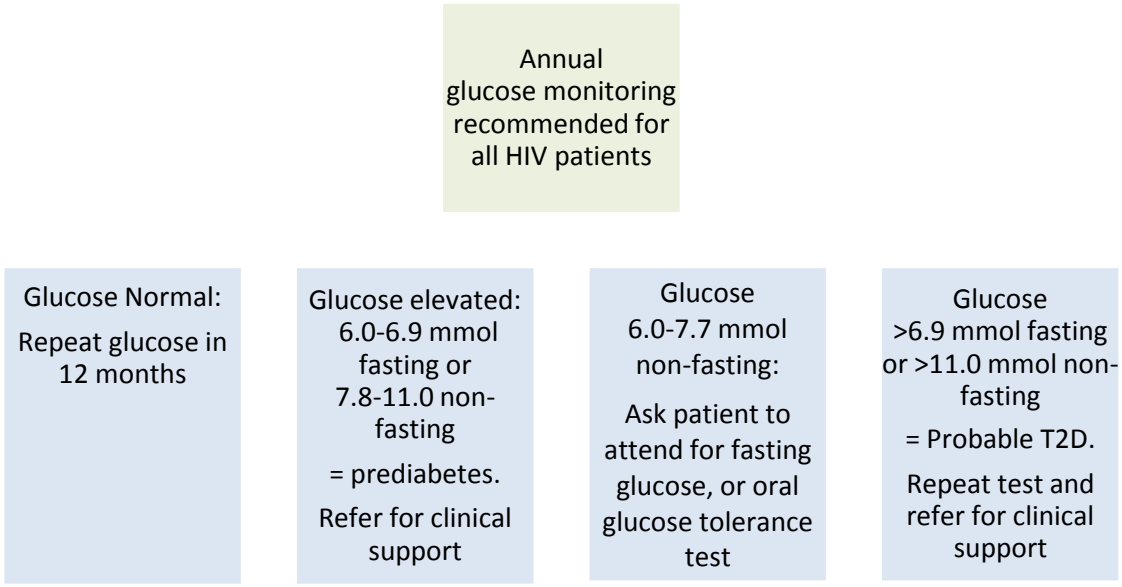
Clinical Challenges:

PLWH with T2D may have a poorer response to diabetes treatments compared to HIV negative individuals (Han et al., 2012). The recently-developed ARV dolutegravir interacts with metformin requiring dose adjustment (Zong et al., 2014), and the use of metformin in patients with lipoatrophy can lead to worsening of facial wasting (Kohli et al., 2007). Hyperglycaemia in HIV increases the risk of developing tuberculosis infection (Achhra et al., 2014). HIV patients with IR are less likely to respond to hepatitis C treatments (Vachon et al., 2011) and IR increases hepatocellular carcinoma risk in those with HIV / Hepatitis C coinfection (Salmon et al., 2012). Finally, IR in HIV patients is associated with poorer neuropsychological performance (Valcour et al., 2012).

1.5.6 Care Guidelines for HIV and Type 2 Diabetes Comorbidity

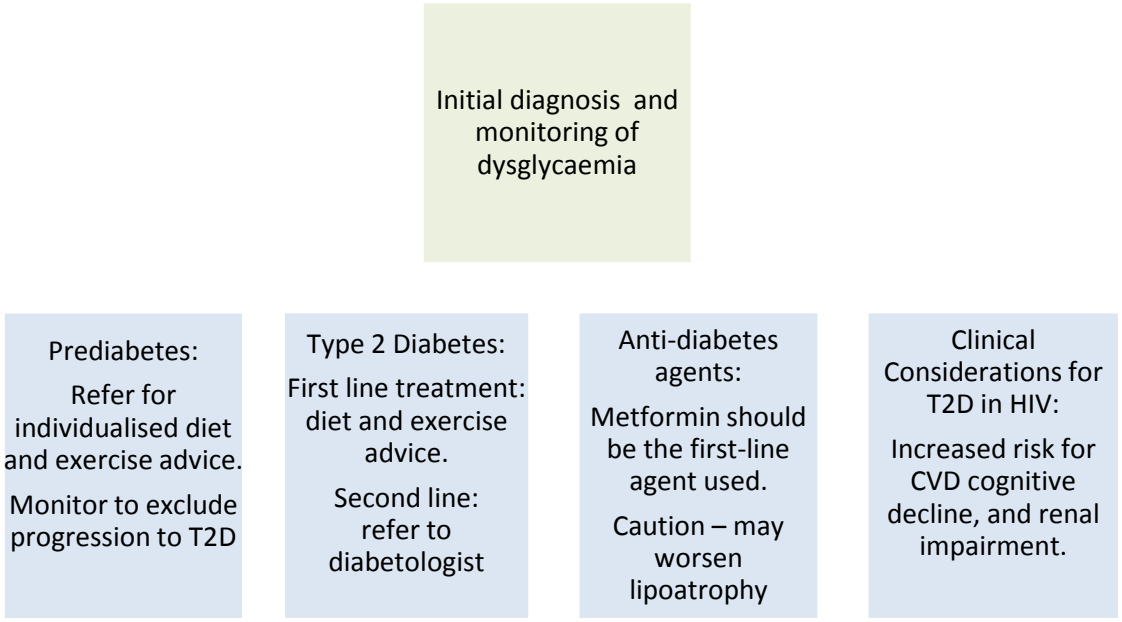
To date no clinical guidelines have been published or developed specifically for those with both HIV and either prediabetes or T2D. The British HIV Association (BHIVA) produces guidelines and standards of care for PLWH in the UK and has published guidelines on screening for metabolic conditions (Asboe et al., 2012); those pertinent to screening for disturbances in glucose homoeostasis are summarised in Figure 3. The European AIDS Clinical Society (EACS) has used guidelines for clinical care of T2D in the general population for HIV patients living with T2D (Lundgren et al., 2008, Ryom et al., 2016). EACS acknowledges the lack of published HIV-specific research in this field. These guidelines are summarised in Figure 4. I performed a search of other national and international HIV treatment or management guidelines, and this revealed no specific mention of diabetes. These guidelines included the WHO (World Health Organisation, 2015), the International Antiviral Society (Gunthard et al., 2014), the National Institute of Health in the USA, the Thai National HIV Guidelines (Manosuthi et al., 2015) and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine. The Southern African HIV Guidelines also do not mention specific care guidelines, but do recommend routine screening of blood glucose given that the pro-glycaemic NRTIs zidovudine and stavudine remain in local use (Meintjes et al., 2015).

Figure 3: UK Guidelines for Screening for Dysglycaemia in HIV.



Source: (Asboe et al., 2012)

Figure 4: European Guidelines for Clinical Care for Dysglycaemia in HIV.



Source: (Ryom et al., 2016)

1.6 Diet and Exercise in HIV

Cohort Studies:

There have been a number of prospective cohort studies that have recognised distinct dietary patterns in PLWH. Researchers aimed to correlate aspects of dietary intake with obesity in an American HIV cohort (Hendricks et al., 2006). Total and saturated fat intakes were significantly higher than recommended levels, with fibre intake reducing incrementally as BMI increased. In another study from the same cohort, researchers reported that patients without lipodystrophy had a significantly higher fibre intake compared to those with lipodystrophy (Hendricks et al., 2003). In the only study published to date to report dietary intakes in a UK HIV cohort, the majority of participants consumed higher than recommended levels of total and saturated fats, and those with lipodystrophy had lower fibre intakes (Klassen and Goff, 2013). In a Croatian study, adherence to the Mediterranean diet was positively correlated with reduced atherosclerotic plaque formation in both HIV positive and HIV negative participants (Višković et al., 2013). Finally an investigation of diet and insulin resistance recruited HIV positive women from San Francisco and Chicago. Using HOMA-IR to assess insulin resistance, statistically significant correlations were observed between both high intensity exercise and higher incomes in those with lower levels of insulin resistance, and between higher consumption of sweets and higher levels of insulin resistance (Hessol et al., 2013).

Interventions:

A literature search retrieved a small number of diet and physical activity intervention studies for PLWH published since the introduction of HAART in 1998, presented in Table 1.10. The majority of interventions were designed to prevent or treat dyslipidaemia although six of the twelve did additionally measure markers of glucose homoeostasis. In a meta-analysis with a CVD focus, investigators found evidence of a weak non-significant pooled effect of dietary interventions on cholesterol fractions but a significant effect on reducing triglyceride levels, with a greater effect when omega-3 supplements were added (Stradling et al., 2012).

In a small study based in Boston, researchers recruited HIV positive adults with metabolic syndrome between 2003 and 2005 (Fitch et al., 2006). The study aimed to investigate the effect of diet and exercise on the components of the metabolic syndrome and their combined effect in terms of classifying participants with the syndrome. Participants were randomised to

intervention (n=12) or usual care (n=16). The intervention was highly intensive: weekly individual sessions with a dietitian plus 3 hours supervised exercise per week over a 6 month period. At baseline, dyslipidaemia and hypertension were the principal contributors to metabolic syndrome. Participants' baseline mean fasting glucose of 5.05 mmol/l increased to 5.22 mmol/l after 6 months. Compared to usual care, the intervention achieved small but significant changes in HbA1c, with a 0.2% unit rise observed in the control group. Significant reductions were also observed in waist measurement and systolic blood pressure, but not weight, glucose, triglycerides or an increase in HDL. All participants remained classified as having metabolic syndrome. The same researchers later published results from a more developed intervention study based on the same cohort (Fitch et al., 2012). This study aimed to investigate the effect of diet, exercise and metformin on markers of cardiovascular disease. Participants were randomised to: metformin alone, metformin plus lifestyle, lifestyle plus placebo or placebo alone. The lifestyle intervention was highly intensive, mirroring the previous study. Compared to baseline, there was no significant change in HbA1c observed between the 4 arms. There was a significant reduction in insulin resistance measured by HOMA-IR in the metformin plus intervention arm only. Other significant findings included metformin reducing progression of coronary artery calcification whereas lifestyle did not.

A Danish study aimed to investigate the effects of a 16-week supervised endurance or strength training intervention on insulin sensitivity specifically in HIV positive men with lipodystrophy. Investigators found both modalities significantly improved peripheral insulin sensitivity (Lindegaard et al., 2008).

In summary, of the twelve studies presented here, five recruited sufficient numbers of participants to draw statistically and clinically significant conclusions. None of these studies were designed with a primary outcome to measure the effect of diet and exercise on markers of insulin resistance. Of the seven studies measuring markers of glucose homoeostasis as secondary outcomes, two demonstrated a beneficial effect. Interventions were typically intensively delivered over extended periods ranging from daily to monthly visits for up to one year, and as a result translation to clinical practice has proved challenging.

Table 1.10: Diet and Physical Activity Interventions in HIV in the HAART Era.

Cohort	Intervention	Results	Ins. Res.	Ref.
Spain, n=230, HAART, dyslipidaemia	Low fat diet for 6 months	Reduced total cholesterol, TGs and weight, strongest effect in those on protease inhibitors	No	1
Brazil, n=30, HAART, lipodystrophy	Low fat diet plus aerobic exercise versus low fat diet alone, 12 weeks	Reduced body weight, and waist to hip ratio in both groups, no change in lipids	No	2
Brazil, n=83, naïve	NCEP diet, 4 sessions over 12 months post HAART	Diet prevented weight gain & dyslipidaemia seen in control arm	No	3
USA, n=191, raised triglycerides	NCEP diet, 4 visits, 6 months, supervised exercise 3/week, plus niacin and fenofibrate	Diet and exercise plus niacin and fenofibrate conferred strongest effect on lipids	No	4
Hong Kong, n=48, HAART	Mediterranean versus low fat, low cholesterol diet, 4 sessions over 12 months	Mediterranean diet – total cholesterol ↑ from 4.6 to 5.1 mmol/l; Low fat diet – triglycerides ↓ from 1.90 to 3.22 mmol/l	No	5
USA, n=18, women, BMI>30	Weekly group diet sessions, and 90mins supervised exercise 3/week, 12 weeks	Mean 6.7kg weight loss, but no improvements in fasting glucose, insulin sensitivity or lipids	Yes	6
USA, n=28, HAART	6 months weekly diet advice, 3 hours exercise/week	Intervention reduced waist, BP and HbA1c but not lipids	Yes	7
Denmark, n=20, men with lipodystrophy	Sedentary men, 2 arms: strength or endurance training, supervised 3/week for 16 weeks	Both arms improved insulin sensitivity and ↑ HDL. Endurance training ↓ LDL, Strength training ↑ LBM, ↓ triglycerides	Yes	8
USA, n=54, HAART, BMI 19-30	Usual care or omega-3 supplements plus lipid-lowering diet plus meals for first 3/16 weeks	Intervention significantly reduced triglycerides, but not other lipid fractions or any markers of insulin resistance	Yes	9
Rwanda, n=187	Supervised exercise 3/week for 6 months	Intervention reduced waist and weight but not HOMA-IR	Yes	10
USA, n=50, HAART, metabolic syndrome	4 arms, 12 months: Metformin/placebo with diet/exercise or nil. Weekly diet, exercise 3/week	Lifestyle plus metformin had greatest effect on artery calcification and reducing HOMA-IR, mostly driven by metformin	Yes	11
Thai, n=59, ↑LDL	Individualised dietary, 7 sessions over 6 months	Reduced LDL and triglycerides in intervention arm vs usual care	No	12

Notes: Ins. Res. = Insulin resistance measured in this study, yes/no; NCEP = National Cholesterol Education Programme; BP = blood pressure; LBM = lean body mass.
References: 1 - (Barrios et al., 2002); 2 - (Terry et al., 2006); 3 - (Lazzaretti et al., 2012); 4 - (Balasubramanyam et al., 2011); 5 - (Ng et al., 2011); 6 - (Engelson et al., 2006); 7 - (Fitch et al., 2006); 8 - (Lindegaard et al., 2008); 9 - (Woods et al., 2009); 10 - (Mutimura et al., 2008); 11 - (Fitch et al., 2012); 12 - (Chotivichien et al., 2016)

Source: Review by A Duncan

1.7 Behaviour Change

The effectiveness of diet and exercise interventions can be measured by the degree of behaviour change achieved by participants. In this section I have presented a brief overview of behaviour change theory and a review of enablers and barriers to lifestyle change as background to help explain methodologies chosen for the pilot intervention.

1.7.1 Behaviour Change Theories and Practice

Changing human behaviours is fundamental to achieving optimal health (Fisher et al., 2011). Behaviour can moderate external or genetic influences and impact on health. Interventions to change behaviour have the potential to prevent or manage disease, to impact on quality of life and to improve health at the individual and population levels. However, it is recognised that sustaining positive behaviour change can be highly challenging. Investigators studying a range of lifestyle behaviours found the most successful behaviour change was smoking cessation following diagnosis of heart disease, where 40% quit. This contrasted with those recently diagnosed with T2D where regular exercise rates increased among 7% of those with higher education, and declined among those with lower education levels (Newsom et al., 2012).

There is a wealth of literature describing theories of health behaviours. A recent review listed 83 different theories and models, including social cognitive theory, theories of reasoned action and planned behaviour, and the health action process model (Michie et al., 2011a). For practical reasons I have chosen to work with the COM-B (Capability, Opportunity, Motivation – Behaviour) behaviour change model (Michie et al., 2011b). This was developed to assist health researchers identify relevant techniques to support delivery of interventions.

The COM-B wheel has three layers: sources of behaviour, intervention functions and policy categories. *Capability* to change behaviour encompasses both psychological and physical capacity to engage in an activity, including the necessary knowledge, skills and tools. *Opportunity* includes physical and social aspects enabling, prompting or facilitating a behaviour. As well as conscious thoughts and goals *Motivation* also encompasses unconscious habits. The author identifies nine intervention functions: education, persuasion, incentivisation, coercion, training, restriction, environmental restructuring, modelling, and enablement. Finally the policy functions describe the processes involved in implementing an intervention once it has been tested.

1.7.2 Enablers and Barriers to Diet and Exercise Change

Successful behaviour change is dependent on utilisation of enablers or motivations and overcoming barriers to change, some of which may be specific to the disease, illness or health condition experienced by the individual (Murray et al., 2013). I conducted a review of qualitative research studies investigating enablers and barriers to adopting diet and physical activity change and have presented this in Table 1.11. The search was limited to reports published between January 2010 and December 2015 characterising enablers and barriers to diet or physical activity change from participants in intervention studies. The search identified 12 publications, two of which were systematic reviews. All research papers cited collected data from participants through in-depth interviews.

For analysis and comparison, enablers and barriers can be categorised using the Theoretical Domains Framework (TDF) (Cane et al., 2012), as can techniques used to change them. There are 14 domains, and these have been matched against behaviours listed in Table 1.11:

1. Knowledge
2. Skills
3. Social role and identity
4. Beliefs, capabilities and self-confidence
5. Optimism
6. Beliefs about consequences and outcomes
7. Reinforcement, incentives and punishment
8. Interactions
9. Goals
10. Memory, attention and decision processes
11. Environmental context and resources
12. Social influences and group norms
13. Emotions, anxieties and fears
14. Behavioural regulation and self-monitoring

The majority of enablers and barriers to diet and exercise change elicited from the literature review fall into categories 4, 6, 10, 11, 12 and 14.

Table 1.11: Review of Enablers and Barriers to Diet and Exercise Change

Enablers		
Factor (TDF Domain)	**Description**	**Refs**
Knowledge/education (1)	New understanding, for example calories in food, benefits of exercise	6
Planning (2)	Planning ahead facilitates both dietary change and exercise opportunities	1
Value of change (3)	Admiration of active people, or desire to serve as an example to others	4
Coping positively with setbacks (4)	Experience of setbacks acknowledged as disappointing but used to spur on to renew efforts to achieve goals	2
Knowledge of illness (6)	Better understanding of the consequences of illness (CVD) drives behaviour change	7
Family history (6)	Family history of illness (Diabetes)	3
Desire to improve health (6)	Diet and exercise used as a means to improve overall health	1
Drawing on success (7)	Previous experience of success (weight loss, smoking) as a driver to change behaviours	2
Future focus (9)	Motivation driven by future goals, for example protecting family time	1
Goal setting (9)	Goal setting acts as a motivator	5
Motivation/willpower (10)	Determination and discipline to succeed drive behaviour change and achievement of goals	1
Mindfulness (10)	Mindfulness approaches facilitate change, for example attention to healthy food choices	6
Cultural sensitivity (11)	Education materials in participant's own first language; culturally appropriate diet and physical activity advice	3
Local facilities access (11)	Exercise facilities accessible in own local environment	8
Tools, technical equipment and aids (11)	Food scales, pedometers, exercise aids, technologies, apps, self-completed records or diaries, all reported to promote successful behaviour change	1
Accountability (12)	Accountability to individuals or groups external to the study	1
Encouragement and support (12)	Exercising together with someone, support from family or employer, making common decisions	1
Pleasure (13)	Fun, wellbeing, and social interaction experienced from exercising	8
Flexibility (14)	Allow flexibility in approach, for example treats in moderation	2
Portion control (14)	Active regulation of portion size, particularly outside of usual routines	6
Daily exercise (14)	Incorporating physical activity into own routine of daily life	4
Lifestyle adaptation (14)	Successfully incorporate change into usual routines of daily living	2
Notes: TDF - Theoretical Domains Framework		

Barriers		
Factor (TDF Domain)	**Description**	**Ref**
Isolation – personal (3)	Lack of support from others in immediate relationships, socially, societally or professionally	7
Body image (3)	Concerns about physical appearance limit exercise (cancer)	9
Not interested (4)	No interest in adopting physical activity at all, or achieving physical activity goals	4
Poor physical health (4)	Pre-existing health challenges, such as fatigue, stroke, musculoskeletal injury or disease, pain, incontinence	1
Lack of future focus (6)	Unfavourable future perspective (cancer survivors) limits motivation to change behaviour and achieve goals	9
Fear - current illness (6)	Fear of exacerbating current illness through physical activity (cancer) and increasing healthier food intake (kidney disease)	
Denial of ill-health (6)	Denial of severity of illness (CVD) limits motivation to change	7
Fear of injury (6)	Fear of injury resulting from exercise (not related to specific illness or condition)	8
Negative reactions (8)	Intentional or unintentional comments or actions from others	6
Lack of guidance (8)	Lack of guidance from health professionals or insufficient guidance provided in study design	7
Difficulty changing (10)	Difficulty in doing without usual foods, changing to healthier alternatives	5
Lack of willpower or self-control (10)	Although initial motivation may have been high, relapse of previous behaviours occurs	5
Bad weather (11)	Seasonal or unexpected bad weather inhibits outdoor physical activity	1
Isolation – distance (11)	Geographically distant from healthcare centre or site of intervention	7
Cost (11)	Healthier foods perceived as being more expensive than usual foods	1
Lack of time (11)	No time for exercise - family, social or occupational constraints	4
Cultural barriers (12)	Fasting (Ramadan, Lent, routine fasting), sharing of traditional sweets (South Asian communities), under-estimating BMI among Blacks (USA), social valorisation of obesity as markers of wealth and success in males and fertility and attractiveness in females (Africa)	10, 11
Poor Mental Health (13)	Anxiety, depression and other mental health challenges diminish ability to change behaviour and achieve goals	9
Not coping, setbacks (13)	Demoralised by poor progress or relapses	2
TDF: Theoretical Domains Framework. **References:** 1 - (Murray et al., 2013); 2 - (Stead et al., 2015); 3 - (Morrison et al., 2014); 4 - (Korkiakangas et al., 2011); 5 - (Hammarstrom et al., 2014); 6 - (Metzgar et al., 2015); 7 - (Murray et al., 2012); 8 - (Clarke et al., 2015); 9 - (van Putten et al., 2016); 10 - (Cohen et al., 2013); 11 - (Hendley et al., 2011); 12 - (Oyekanmi and Paxton, 2014).		

Source: Review by A Duncan

1.7.3 Diet and Exercise Behaviour Change in People Living with HIV

Few studies have been published reporting issues regarding enablers and barriers to diet and exercise behaviour change in PLWH. Researchers conducting a questionnaire-based study in the UK reported that among 92 HIV positive Black African and Black Caribbean origin patients, being overweight was not considered to be a health concern (Bradbeer and Bakar, 2008). In a study based in New York a purposive sample of 123 HIV positive people was invited to take part in focus groups, exploring expectations, perceptions and beliefs related to a healthy lifestyle (Capili et al., 2014). Barriers to healthy behaviours included financial barriers to making healthier food choices, using obesity to mask HIV infection and isolation. Facilitators included good patient-provider communication, peer support and maintaining a positive attitude. The authors suggest that financial barriers are the primary barrier and social support the primary facilitator. In South Africa, participants in an intervention to increase physical activity were interviewed regarding enablers and barriers to change (Roos et al., 2015). Barriers identified included low energy levels, stress, family responsibilities, poor weather, domestic abuse and crime. Facilitators included support from friends and family, religious practices, and access to parks. From the COM-B model, these three studies highlight a lack of motivation and capability to change as barriers, and opportunity as well as motivation from self and others as enablers.

There is a series of reports regarding body image in people living with HIV. People experiencing lipodystrophy report psychological distress associated with their appearance (Huang et al., 2006, Blashill and Vander Wal, 2010). In a questionnaire-based study of 103 HIV positive women in New Orleans investigators suggest that African-American women prefer a large body size and believe they will not be perceived as sick if they gain weight (Clark et al., 1999). Increased BMI is associated with negative body image in older HIV positive men and White HIV positive women (Sharma et al., 2007).

Enablers and barriers to lifestyle change in people living with HIV partly correspond with those characterised in Table 1.11. There additionally appear to be HIV-specific factors, and these require further characterisation.

1.8 Estimating Disease Risk

Disease risk prediction tools and calculators use individual data entered into an algorithm to estimate disease risk. There are a number of tools developed for use in diverse or particular cohorts. Given the increased risk of T2D and CVD in PLWH (see section 1.3.4) predicting disease presents an opportunity to reduce potential morbidity. CVD prediction tools may underestimate risk in PLWH (NICE, 2014b).

The Framingham Risk Score published in 1998 may inaccurately estimate CVD risk in people living in the UK (Brindle et al., 2003, Mahmood et al., 2014). Two CVD risk tools developed and validated in UK populations are the JBS3 score developed by the UK's joint societies (Joint British Societies Board, 2014), and the QRISK2 calculator derived from UK primary care patients (Hippisley-Cox et al., 2008). QRisk2 is the tool endorsed and currently recommended by NICE to predict CVD risk in the UK (NICE, 2014b).

The HIV-specific D:A:D CVD risk score was developed from the prospective observational D:A:D study, a collaboration of 11 cohorts observing HIV patients from 212 clinics in Europe, Australia and the United States (Friis-Moller et al., 2010). Investigators have compared the efficacy of traditional CVD risk tools such as Framingham and the European Systematic Coronary Risk Evaluation Score (SCORE) with the D:A:D CVD risk score in a European cohort of HIV patients and observed only a moderate level of agreement (Begovac et al., 2015). Observed agreement was better in a Brazilian cohort (Nery et al., 2013). However, in a Thai cohort Framingham predicted high risk in 10% compared to 1% using D:A:D (Edwards-Jackson et al., 2011).

A range of tools have been developed to predict risk of developing T2D including the Finnish FINDRISC tool (Saaristo et al., 2005), the Framingham Diabetes Risk tool (Wilson et al., 2007), the Cambridge Diabetes Score (Griffin et al., 2000), the QDScore based on data from GP practices in the UK (Hippisley-Cox et al., 2009) and the Leicester Risk Assessment tool (Gray et al., 2010). Additionally an HIV-specific diabetes risk prediction equation has been developed from the D:A:D study (Petoumenos et al., 2012). The investigators compared the D:A:D and Framingham tools and found that Framingham over-predicted diabetes events in PLWH.

1.9 Epistemology

In this section I aim to interpret how my beliefs and experience have influenced my approach to conducting this research project. The key philosophical issues of ontology and epistemology underpin the individual's approach to research. Ontology, the nature of the world and what there is to know about it, can be divided into two broad positions: realism and idealism. For realists external reality exists independently of beliefs or understandings and can be observed and known directly, approximately, or in the case of materialism in relation to economic or physical features. For idealists no external reality exists independently of beliefs or understandings (Rachael Ormston, 2014). In terms of research I place myself towards the realist end of the spectrum. Although I generally believe that phenomena identified by research reflect reality, I am open to the possibility that alternative explanations may exist, and in this regard I would feel comfortable being labelled a "critical realist" (Bhaskar, 2013) or a "cautious realist" (Blaikie, 2007).

Epistemology concerns the basis of knowledge and how the individual learns about reality. An inductive approach builds knowledge through observation, allowing development of theories or laws. Deductive logic uses theory as a starting point, developing a hypothesis for testing. Previous authors have argued that either a purely inductive or purely deductive approach is practically unachievable (Blaikie, 2007). I would agree with this as in modern society there are few avenues for research to proceed without prior exposure to ideas or information. I place myself towards the inductive end of the spectrum as, for me, observations in clinical practice have generally led to development of hypotheses.

A key epistemological issue in research is the relationship between the investigator and the participant, and the degree to which this relationship may affect observation and results. This concept is separate to the Hawthorne effect where research participation itself can affect outcomes or data produced (McCambridge et al., 2014). Where the phenomena under investigation are entirely unaffected by the investigator the results are free of value on their part and the report can be objective. Where the participants are affected by the investigator or the research process, an objective account cannot be produced and results are value-mediated through the researcher. Between these polarities lies the position of empathic neutrality. Researchers are encouraged to be transparent about their assumptions, values and bias at all stages of the investigation, enabling a neutral non-judgemental approach (Blaikie, 2007).

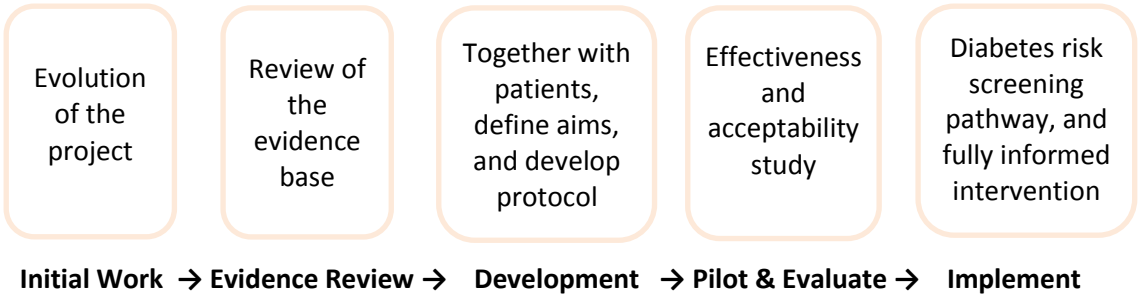
My research practice is undoubtedly influenced by clinical practice and observations of patients, as mentioned already. Additionally, I practice with a patient-centred approach. Although beneficial for the patient and research participant, this approach has potential to be detrimental to the research process. For example, when weighing up the benefits and challenges of a technique to measure an outcome, I might be persuaded to choose the technique with the least burden for participants even if this results in a lower quality of research output. With my prior experience in healthcare management I am acutely aware of key financial and quality challenges facing the NHS and this has potential to lead to prioritisation of interventions or approaches with a lower financial burden. I am aware that I place importance on health research being clinically relevant. Finally, in terms of qualitative and quantitative research, my background in quantitative research is counterbalanced by immersion in behaviour change in clinical practice.

1.10 Design, Hypothesis, Aims and Objectives

With the risk of developing T2D in a treatment-experienced cohort reported as up to four times higher than matched HIV negative controls (Brown et al., 2005), it was calculated that unless prevention could be achieved, between 2016 and 2026 as many as 15,000 new HIV-associated T2D diagnoses may present in the UK (Health Protection Agency, 2012, Dyson et al., 2011). Lifestyle interventions are highly effective at preventing the progression from prediabetes to T2D reducing incidence by up to 59% (Walker et al., 2010, Goff and Duncan, 2010). Therefore, the potential that despite the actions of HIV infection and antiretroviral medicines a lifestyle intervention in patients with HIV-associated prediabetes would improve insulin sensitivity and other metabolic parameters proved a distinct and clinically important avenue for investigation and provided the underpinning theory for this research project.

Given the growing impetus to develop a pragmatic and affordable T2D prevention intervention and the complexity of the cohort to be investigated, the study design was developed using the Medical Research Council (MRC) guidance on development, evaluation and implementation of complex interventions to improve health (Craig et al., 2008), and the work presented in this thesis represents the first four stages:

Figure 5: MRC Framework for Developing Complex Interventions.



1.10.1 Project Design

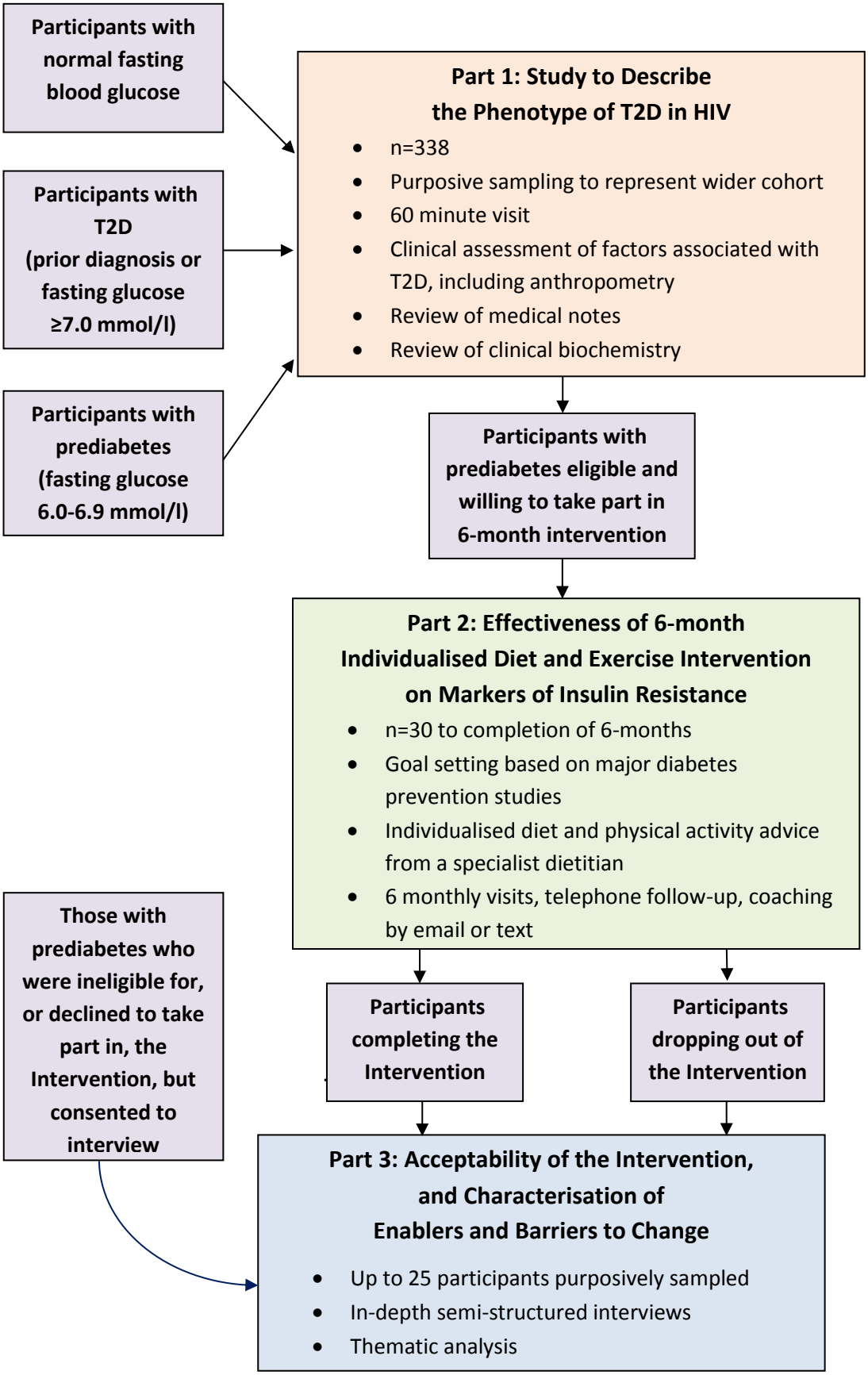
The portfolio of research presented in this thesis aimed to investigate the following:

- Factors associated with prediabetes and T2D in an HIV cohort in the UK
- Changes over time, through comparing new data with that collected from the same cohort 10 years previously
- The effectiveness and acceptability of an individualised 6-month diet and exercise intervention designed to reduce markers of insulin resistance in those stable on antiretroviral therapy and with prediabetes
- Enablers and barriers to lifestyle change in PLWH and prediabetes

I designed the portfolio of research in three distinct but interrelated parts, with the potential for participants recruited progressing from one part to another, as outlined in Figure 6.

- **Part 1: The Phenotype of Dysglycaemia in HIV**
  A cross-sectional study designed to describe the phenotype of T2D in HIV. Compare findings with data collected 10 years earlier
- **Part 2: Diet and Physical Activity Intervention**
  A pilot intervention to investigate the effectiveness of individualised advice to change diet and exercise on markers of insulin resistance in those with prediabetes
- **Part 3: Qualitative Research Study**
  A qualitative investigation of the acceptability of the interventional study, enablers and barriers to lifestyle change, and attitudes to participation in research

Figure 6: Summary Flowchart of Study Design.



1.10.2 Underpinning Theory

People living with HIV and treated with ARV medicines are at a higher risk of developing T2D. The aetiology of insulin resistance in PLWH is complex and multifactorial, including a range of fixed and modifiable contributory factors. The small number of prior lifestyle interventions in PLWH have had either no effect or a small effect on insulin resistance, even with intensively delivered support. Despite this, there is potential for diet and exercise change to reduce insulin resistance in PLWH given the increasing prevalence of obesity in this cohort.

1.10.3 Hypotheses

For each of the three parts of the study presented in this thesis, research questions were designed to test the following hypotheses:

1. In HIV patients, BMI, diet, physical activity and a range of other factors are independently associated with impaired fasting glucose and type 2 diabetes when compared to patients with normal fasting glucose
2. A 6-month intervention of diet and physical activity advice, individualised to address ethnic and socioeconomic differences, will result in a clinically significant reduction in glucose incremental area under the curve over a three-hour meal tolerance test, in PLWH with impaired fasting glucose
3. PLWH at risk of type 2 diabetes experience both HIV-specific and general enablers and barriers to behaviour change

1.10.4 Aims and Objectives

1. **The Phenotype of Dysglycaemia in HIV**

   Aims:

   To phenotype dysglycaemia in this cohort, and describe how this has changed over time.

   Primary objective:

   To compare a range of demographic, anthropometric, medical, diet, activity and socioeconomic factors by glycaemic status in order to phenotype dysglycaemia in HIV.

Secondary objectives:

- To compare data collected in this study with historic data collected 10 years previously principally from our cohort in the CREATE study (Aboud et al., 2010) and with data from the general population in London and the UK
- Given the piloting of a diet and physical activity intervention, to assess in particular the relationship between dietary intake and physical activity and dysglycaemia
- To assess associations between BMI, gender and ethnicity
- To assess which tools are most accurate for predicting CVD and T2D risk in this cohort using data from the phenotype study

2. Diet and Physical Activity Intervention

Aims:

To assess the effectiveness of individualised diet and physical activity advice on markers of insulin resistance in people living with both HIV and prediabetes.

Primary objective:

To measure the change from baseline at 6 months for glucose incremental area under the curve, measured in a 3-hour meal tolerance test.

Secondary objectives:

- To measure the change from baseline at 6 months for insulin incremental area under the curve measured in a 3-hour meal tolerance test, indices of insulin resistance/sensitivity, dietary change, physical activity, lipids, anthropometry and body composition, frailty, blood pressure, CD4 count and HIV viral load, and cardiovascular and diabetes risk
- To measure the effect of the intervention on quality of life
- To measure the effect of the intervention on bowel habits and gut symptoms

3. Qualitative Research Study

Aims:

(1) Investigate the acceptability of the diet and physical activity intervention

(2) Characterise enablers and barriers to behaviour change

(3) Investigate attitudes to participation in medical research

2 METHODOLOGY AND PROCEDURES

> *'the research presented in this thesis was conducted in compliance with the principles of the Declaration of Helsinki 2008 and the Human Tissue Act 2004'*

2.1 Introduction

This chapter details the rationale for design and choice of methodology as well as procedures used in the three studies presented in this thesis, procedures used, and the management approach employed to oversee the conduct of the research (Figure 7).

2.2 Ethical Practice and Approval

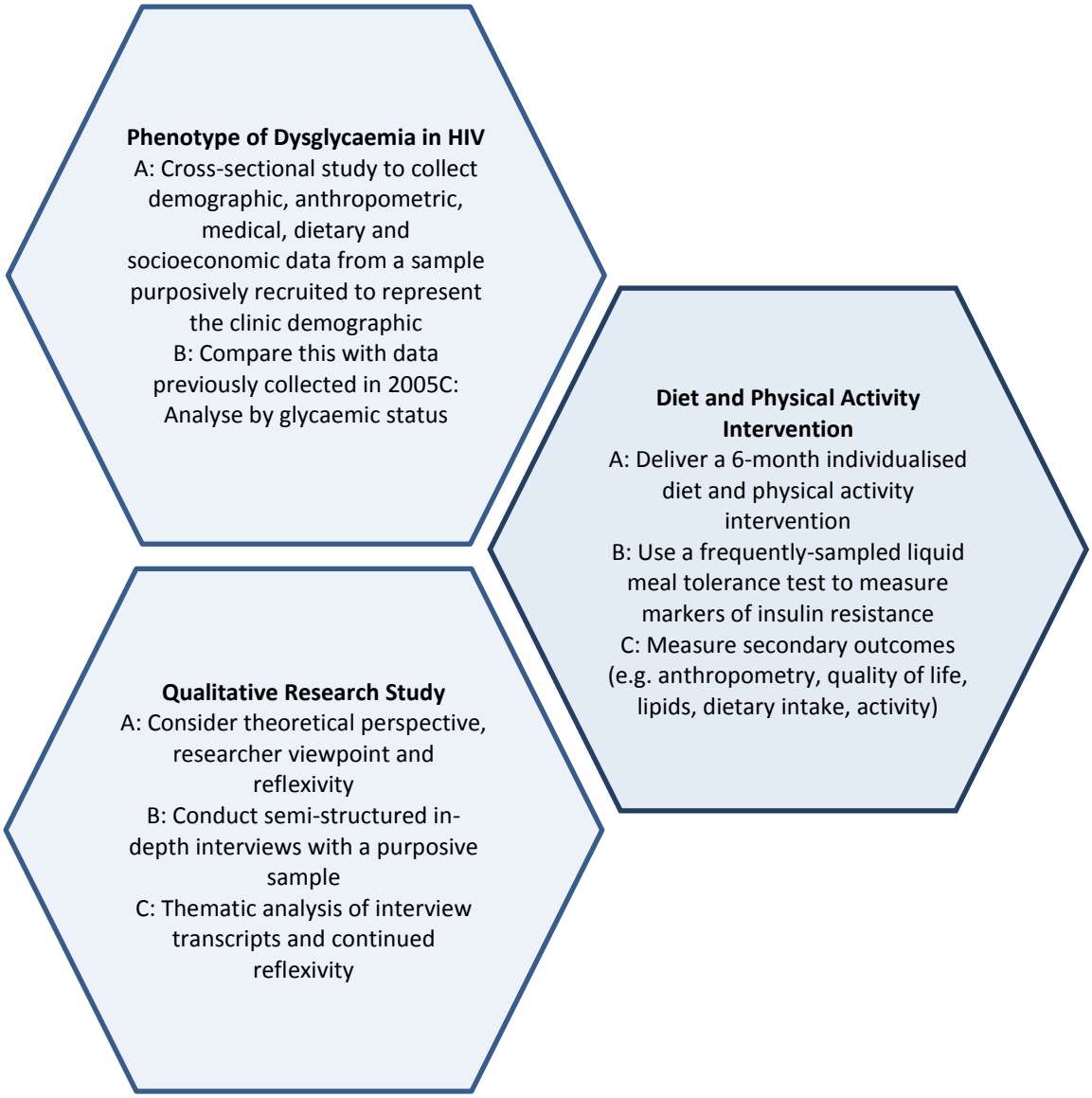
The research presented in this thesis was conducted in compliance with the principles of the Declaration of Helsinki 2008, the Human Tissue Act 2004, and Good Clinical Practice. The protocol was approved by the London-Bromley NHS Research Ethics Committee (REC) on 12/11/2013, ID number 13 LO 1543, and subsequently by the King's Health Partners (KHP) Research and Development. Regular progress reports were submitted to the REC and to KHP.

2.3 Recruitment and Screening

Participants were recruited from HIV outpatient clinics within KHP through self-referral in response to advertising in clinic waiting areas or by referral by members of the clinic healthcare team. The primary site for recruiting participants was the HIV outpatient clinic at St. Thomas' Hospital in central London. Secondary sites, both within the KHP organisation, were

the smaller HIV outpatient clinics at King's College Hospital and the Beckenham Beacon Health Centre in South East London. The poster used to advertise the study is presented in Appendix 1. All potential participants were provided with both a participant information sheet and a consent form (Appendix 2), describing the study and providing sufficient information for participants to make an informed decision about their participation.

Figure 7: Summary of Research Methods Used in the Three Linked Studies



In line with NHS guidance (Health Research Authority, 2016) the participant information sheet and consent form were piloted with the expert patient and HIV positive scientist working group convened for this study to ensure readability, as participant information produced for HIV research studies has been criticised for being at an advanced literacy level inaccessible to many (Collins et al., 2015).

A screening form was used to assess eligibility prior to arranging a meeting to discuss participation and consent. The formal signed consent of participants was obtained before initiating any study procedures. All potential participants had at least 24 hours to read the participant information sheet, understand the protocol, the risks and benefits, and were encouraged to ask questions. However, if the participant expressed a preference to consent at the time of obtaining the information sheet and consent form, they were able to provide consent at that time (Health Research Authority, 2016). In these cases, the researcher contacted the participant 24 hours later to confirm their decision to be involved.

Potential participants were assessed for capacity to consent for themselves (Health Research Authority, 2013). Potential participants without a good understanding of verbal or written English were not invited to take part in any of the three study parts as there was no provision for translation or interpreters within the research budget. Finally, following NRES guidelines, all prisoners were excluded from participation (Charles et al., 2014).

2.4 Research Management

2.4.1 Research Supervision

The research was overseen by a PhD Supervision Committee, with regular meetings scheduled according to KCL policy. More frequent supervision was provided by supervisors and email contact with collaborators. Research quality was also overseen by the sponsor, the Research and Development department at Guy's and St. Thomas' Hospital. The trial was open for audit and inspection. Regular progress reports were submitted to the NIHR, KCL, the REC, and to the Sponsor.

2.4.2 Participant Welfare

Prior to commencement of the research, an adverse event (AE) was defined as any symptom, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries were regarded as AEs. Abnormal results of laboratory or diagnostic procedures were also considered to be AEs if a) they were associated with a serious adverse event, clinical signs or symptoms, b) led to additional treatment, or c) were considered to be of clinical significance. A serious adverse event (SAE) was defined as: fatal; life-threatening; required or prolonged a hospital stay; or resulted in significant disability. As lead investigator I oversaw the safety of the study, including assessment and appropriate reporting of AEs. Medical monitoring included a regular assessment of the number and type of SAEs, overseen by physicians. All AEs were recorded in the participants' case histories. Risk assessment was performed prior to commencing the study (Table 2.1).

Table 2.1: Assessment and Mitigation of Risk in Intervention Procedures

Issue	Potential Risk	Mitigation
Phlebotomy	Venous cannulation can present a small risk to the participant, e.g. pain, haematoma formation, and to the individual undertaking the procedure (principally needle stick injuries)	An experienced and competent research nurse inserted the cannula. In the event of a failure an experienced alternative research nurse or doctor was asked to assist
Fasting	Certain ARVs must be administered with food to ensure adequate absorption	Those who normally took morning ARVs were asked to take them with the test meal
Physical Activity	Participants were encouraged to increase physical activity levels as part of the intervention, potentially leading to discomfort on over-exertion	Advice given mirrored that delivered as part of everyday clinical practice. Participants were advised to be mindful of safety and tolerance
Mental Health	Some participants may fear that losing weight might lead to disclosure of their HIV status	On-call access to a psychologist and counsellors was available
	Participants were asked to complete an HIV-specific quality of life questionnaire with potentially upsetting questions	On-call access to a psychologist and counsellors was available
	During the interviews participants may say something that they regret	Participants were reminded they could ask for any section of the recording to be deleted

Source: A Duncan

2.4.3 Participant Remuneration

As directed by the NHS Research Ethics Committee the following remuneration was provided to participants:

- Reimbursement in full of all travel expenses
- Breakfast (£3) for any fasting visits
- £25 for attending for the FSLMTT on days 1 and 180
- £20 for attending for interview

2.4.4 Data Management

Source data was defined as the clinical findings, observations, laboratory and test data, and other information contained in source documents. Source documents were the original records including medical records, pharmacy dispensing records and recorded data from automated laboratory systems. Participant data was anonymised and coded. Data was stored on a password-protected laptop and on password-protected memory keys. All records were stored in compliance with the Data Protection Act (Information Commissioner's Office, 2015).

It was attempted to minimise missing data throughout the design of the research protocol. Spurious data deemed to be as a result of a defective piece of equipment was excluded if that test could not be repeated.

2.5 Phenotype of Dysglycaemia in HIV

2.5.1 Rationale for Design

The aim of this cross-sectional study was to phenotype dysglycaemia (prediabetes and T2D) in this HIV cohort and how this has changed over time. Data from a comparable cohort had been collected 10 years previously in the CREATE study (Aboud et al., 2010) and for this project was reanalysed by me. With this in mind 2015 data collection methods were designed to allow comparison, although direct longitudinal comparison was not included in this study.

Consideration was given regarding the method of selecting participants in order that the sample represent the population, and selection bias minimised. In HIV medical research it has proved challenging to recruit women and people from Black and Minority Ethnic groups (Loutfy et al., 2014, Bass et al., 2016, Wolak et al., 2012, Castillo-Mancilla et al., 2014). Additionally, the phenomenon of research fatigue has been described (Pagano-Therrien, 2013). Taken together these two factors could potentially lead to particular sub-groups being underrepresented. To overcome these issues, it was decided to recruit participants using a proportionately stratified random sampling methodology. Ideally, recruiting a sample stratified by factors of interest would result in a cohort being representative of the population.

The principal factor correlated with dysglycaemia is obesity (Hu, 2011). Stratification of the sample by BMI category was considered. However, prior to analysis of data collected in this study the population distribution of obesity in this HIV cohort was unknown. Patients attending HIV outpatients are coded by gender, ethnicity (9 categories) and age, therefore the population distribution of these factors in known. Given their association with dysglycaemia these factors were chosen to construct a purposive, proportionately stratified random sampling methodology.

2.5.2 Power Calculation and Sampling

The hypothesis for this cross-sectional study was that BMI and other factors are independently associated with dysglycaemia. Sample size was calculated using assumptions from a preliminary analysis of the 2005 data (the CREATE study) indicating a prevalence of dysglycaemia of 28% with a mean BMI of 24.9 kg/m^2. With absolute and type 1 errors both set at 5% using the formula $n = \frac{Z^2 \times p(1-p)}{d^2}$ where Z = type 1 error, p = expected proportion in the population, and d = precision or absolute error (Charan and Biswas, 2013), the sample size was calculated to be 339, approximately 10% of those regularly attending outpatients.

To facilitate stratified sampling, anonymised clinical coding data was used to obtain demographic information regarding adult HIV patients who had attended outpatients twice or more within the 12 months prior to commencing the study. This data was subdivided by gender, ethnicity and 10-year age bands. The original 9 ethnicity categories were collapsed

into 4 reflecting the distribution of the population. “Other” ethnicities in the sampling structure included South and East Asians, Latin Americans, and Others, together comprising approximately 10% of the population. The study recruitment target of 339 participants was proportionately entered into a purposive stratified sampling grid (Table 2.2), using methodology from purposive sampling in diabetes surveys (Dowse and Zimmet, 1992). Where the sample in any cell was less than 1% this was rounded up, resulting in a total recruitment target of 340 participants. Selection bias was minimised by screening every third patient on outpatient lists (Levy and Lemeshow, 2008).

Table 2.2: Phenotype Study Stratified Sampling Grid

Age Band (years)		18-29	30-39	40-49	50-59	60-69	70+
Male	**White**	7	17	48	44	33	7
	Black African	1	6	13	11	2	1
	Black Caribbean	1	1	8	8	1	1
	Other	1	9	8	6	3	1
Female	**White**	2	2	2	2	1	1
	Black African	2	12	28	23	5	1
	Black Caribbean	1	1	4	4	1	1
	Other	1	2	2	2	1	1

Source: A Duncan

2.5.3 Inclusion and Exclusion Criteria, Cross-sectional Study

Participants were eligible for participation in the phenotype study as follows:

- HIV positive adults (aged ≥18 years old)

Participants were ineligible as follows:

- If no fasting glucose within the last three months and unable to fast for a single blood glucose test
- Unable to provide informed consent to participate
- Unable to attend for a 30-minute research assessment and data collection visit
- Unable to communicate in English
- Currently serving a custodial sentence

2.5.4 Methods of Data Collection, Cross-sectional Study

Data collection in 2014 and 2015 was designed as far as possible to be comparable to that collected 10 years earlier. Methods of data collection in 2004-2005 for the CREATE study have been described previously (Elgalib et al., 2011). In summary, potential participants were referred by the healthcare team, screened and consented. A range of demographic, medical, biochemical and anthropometric data outlined in Table 2.3 was collected during a short clinical assessment conducted by healthcare researchers, anonymised and entered into a password-protected Microsoft Excel spreadsheet. As shown in Table 2.3 a wider range of data was collected in 2014-2015 reflecting knowledge of metabolic risk factors which had emerged over the intervening time. All participants attended fasting, and were stratified by glucose measurements or a recorded diagnosis of type 2 diabetes. Those with a prior diagnosis of T2D and those newly diagnosed on this fasting test were combined into a single group "type 2 diabetes". Data was collected through a direct interview corroborated from medical notes and e-records, anonymised and entered into a password-protected Microsoft Excel spreadsheet.

Demographic Data:

Age was recorded on the day of the data collection interview. Self-identified categorisation of ethnicity, country of birth and parental ethnicity were recorded, and together constructed seven groups: White, Black African, Black Caribbean, South Asian, East Asian, Latino and Other. Participants defining themselves as Black British were categorised as African or Caribbean according to parental ethnicity. Gender was self-identified as male or female, with no participants self-identifying as transgender. First and second degree relatives with T2D were recorded, and separately relatives with type 1 diabetes.

Anthropometry:

Height and weight were measured using standardised calibrated electronic equipment, and BMI was calculated and categorised as: underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥30.0 kg/m^2). Waist, defined as the midpoint between the lowest rib and the supra-iliac crest, was measured using a non-stretch tape measure and categorised using ethnic and gender-specific International Diabetes Federation (IDF) criteria (Alberti et al., 2006); these criteria were also used to define metabolic syndrome as described in Table 2.4.

Table 2.3: Data Collected From Cross-sectional Studies in 2005 and 2015

		2005	2015
Traditional Factors Potentially Associated with Type 2 Diabetes	Age	✓	✓
	Gender	✓	✓
	Ethnicity	✓	✓
	Relative with Type 2 Diabetes		✓
	BMI	✓	✓
	Waist	✓	✓
	Gestational Diabetes		✓
	Polycystic Ovary Syndrome		✓
	Socioeconomic Status		✓
	Employment Status		✓
	Higher Education		✓
	Dietary Intake		✓
	Physical Activity		✓
	Hypertension	✓	✓
	Smoking	✓	✓
	Cardiovascular Disease	✓	✓
	Stroke		✓
	Renal Impairment		✓
	Hepatic Steatosis		✓
HIV-related Factors Potentially Associated with Type 2 Diabetes	Duration of HIV infection	✓	✓
	Duration of ARV therapy	✓	✓
	Exposure to ARVs associated with diabetes	✓	✓
	Weight change following initiation of ARVs		✓
	CD4 nadir		✓
	HIV suppression (viral load)	✓	✓
	Lipodystrophy syndrome	✓	✓
	Hepatitis B Co-infection	✓	✓
	Hepatitis C Co-infection		✓
	Vitamin D	✓	✓
	Dyslipidaemia	✓	✓

Source: A Duncan

Table 2.4: Definitions of Central Obesity and Metabolic Syndrome

		Males	Females
Central Obesity (Waist size)	**Europid, African, Caribbean, Arab**	≥94 cm	≥80 cm
	South and East Asian, Latino	≥90 cm	≥80 cm
Metabolic Syndrome: Central obesity plus two or more of the other four factors	**Triglycerides** (Fasting)	≥1.7 mmol/l or specific treatment	≥1.7 mmol/l or specific treatment
	HDL (Fasting)	<1.03 mmol/l or specific treatment	<1.29 mmol/l or specific treatment
	Blood Pressure	Systolic ≥130 or diastolic ≥85 mm Hg or specific treatment	Systolic ≥130 or diastolic ≥85 mm Hg or specific treatment
	Glucose (Fasting)	≥5.6 mmol.l or diagnosis of T2D	≥5.6 mmol.l or diagnosis of T2D

Source: (Alberti et al., 2006)

Socioeconomic Status:

Socioeconomic status was calculated using two methods. The UK National Statistics Socioeconomic Classification (NS-SEC) is the tool currently used by the UK government and most widely in studies of health inequalities; it categorises according to type and status of employment using an online tool (Office of National Statistics, 2010). Categories 1 to 6 comprise higher managers / professionals, lower managers / professionals, intermediate occupations, small employers, technical occupations, semi-routine occupations, and routine occupations respectively. Category 7 combines students, the retired or unemployed. For this study, category 7 was subdivided to record these separately, as PLWH are disproportionately unemployed secondary to chronic illness, with only 47% of Londoners living with HIV employed (Ibrahim et al., 2008). The data collection form is shown in Appendix 7.3.

The MacArthur Socioeconomic Scale uses a Likert scale in order that participants can define themselves in terms of subjective socioeconomic status, firstly within their own self-defined community and secondly more widely (Adler et al., 2000). This scale was chosen as it has the ability to identify people of a lower socioeconomic status who might be well-supported or of a high status within their own community. This has been correlated with better health and reduced mortality (Singh-Manoux et al., 2003). The data collection form is shown in Appendix 7.4. I selected this methodology as many PLWH have been unemployed for extended periods, often since their HIV diagnosis potentially over 30 years previously. However, they may be well-supported within their community (Basavaraj et al., 2010).

In addition to the two socioeconomic status measures participants were asked if they considered themselves to be in a situation of financial struggle. This was self-categorised using three options developed to assess this factor in chronic illness (Surtees and Wainwright, 2007): (a) Quite comfortably off (b) Able to manage or (c) I struggle to get by from week to week. Only those who answered (c) were defined as in financial struggle. Finally, attainment of higher education was also ascertained.

Lifestyle Behaviours:

A range of lifestyle factors was recorded in order to characterise the variables needed for CVD and diabetes risk calculations (Hippisley-Cox et al., 2009, Hippisley-Cox et al., 2008, Gray et al., 2010). The number of portions of fruits and vegetables usually consumed per day was recorded as well as hours per week of physical activity defined as exertion greater than usual walking speed. Smoking status was categorised as current, never, or ex-smoker, with number of cigarettes recorded.

Participants were asked to record a 5-day diet diary and were issued a stamped return envelope to increase compliance. The MRC Human Nutrition Unit 5-day diary with photographs to aid recording of portion size was used. Rationale for method of assessing dietary intake is discussed fully in Section 2.6.9. Those participants who did not return completed diaries within 2 weeks were reminded to do so by telephone or email according to their chosen method of communication. A final third reminder was issued one month later to non-responders. Estimated energy expenditure was calculated using Oxford (Henry) equations to compute basal metabolic rate, with a physical activity factor of 1.3 for this relatively sedentary cohort (mean 2.3 hours of activity per week, see Table 3.3) applied to calculate total energy expenditure (Henry, 2005).

Medical Information:

Blood pressure was measured three times by a Vital Signs 300 Series 53000-E4™ electronic sphygmomanometer after at least five minutes of relaxed sitting, and a mean calculated for both systolic and diastolic measures. Hypertension was defined as a mean greater than 140 systolic or greater than 85 diastolic mm Hg of blood, or current use of hypertension medication i.e. those with treated hypertension included within the “hypertension” group (Abbott et al., 1994). Co-morbidities potentially associated with dysglycaemia risk specifically

checked at interview were: cardiovascular disease including myocardial infarction, stroke or transient ischaemic attack, chronic kidney disease, polycystic ovary syndrome, and hepatitis B or C. A history of gestational diabetes was also recorded. These were corroborated from medical notes with those successfully cleared of hepatitis C categorised as negative. Use of statins and corticosteroid medications was recorded. Hepatic steatosis was recorded from medical notes. Hepatic steatosis was assessed using standard clinical definitions by biopsy, MRI scan, or assessed by Fibroscan with an attenuation greater than 250 (Sasso et al., 2016).

HIV Parameters:

Known duration of HIV infection was measured from the date of the first positive HIV antibody test, and duration of ARV therapy from the date of first use of any ARV. Exposure to ARVs associated with insulin resistance was defined as current or historic treatment with AZT (zidovudine), ddI (didanosine), ddC (zalcitabine), d4T (stavudine), Indinavir, or high-dose Ritonavir (De Wit et al., 2008) (Rasmussen et al., 2012) (Hadigan and Kattakuzhy, 2014). Weight change following initiation of ARVs and CD4 nadir were corroborated where possible from medical notes; those predating 1996 were frequently unobtainable. HIV suppression was defined as current HIV viral load being undetectable (<50 copies per ml). Lipodystrophy syndrome was defined as current or historic by participant recall or physician diagnosis from the medical notes, and date of onset was recorded.

Biochemical Data:

Fasting lipids (total cholesterol, LDL, HDL and triglycerides), and vitamin D were recorded. For this study dyslipidaemia was defined as: total cholesterol, LDL cholesterol or triglycerides above the reference range, or HDL cholesterol below the reference range. The common use of the term dyslipidaemia differs between clinical practice among specialists working in HIV care and diabetes care. LDL and triglycerides are frequently raised in PLWH. HDL can be suppressed or apparently induced by certain ARVs, whereas in diabetes care, triglycerides are often raised and HDL can be low; the HDL to triglyceride ratio is often used as an indicator of metabolic health.

Vitamin D is not regularly measured in this cohort. I anticipated there would be a large proportion of missing data and chose to define this variable as most recent measurement within 3 years of data collection. Additionally Vitamin D measures are subject to seasonal fluctuation. Interpretation of any correlation would be tempered by this.

2.5.5 Disease Risk Modelling

Data was applied to a range of risk prediction tools described previously (Section 1.8). Clinically significant risk thresholds were used as benchmarks for assessing each equation's ability to predict risk and degree of correlation. For CVD risk, the threshold used was 10% or greater 10-year risk, and for T2D, moderate or high risk was used, as moderate risk predicts prediabetes (NICE, 2014b). For estimating CVD risk the Framingham, QRisk2, JBS and D:A:D equations were used. I chose these tools as, despite reports of underestimating CVD risk in HIV patients, Framingham remains the best known estimation tool. QRisk2 is recommended by the British HIV Association. JBS remains in use in the primary care setting, and although based on QRisk2 data this tool was designed to estimate lifetime risk as opposed to shorter-term 10-year risk in the other tools, and may be useful in a younger cohort such as those living with HIV. The D:A:D equation is the only HIV-specific prediction equation developed to date.

For estimating T2D risk, the QDRisk, Cambridge, Leicester, FINDRISK, and D:A:D equations were used and compared. Diabetes risk tools are used less frequently in clinical practice compared to CVD risk tools. However, this study offered an important opportunity to test the sensitivity and specificity of each tool and consider implications for clinical practice (Peters et al., 2013a).

2.5.6 Statistical Analysis, Cross-sectional Study

Data for both time points 2005 and 2015 was imported from Microsoft Excel and analysed using IBM SPSS. Distribution of the data was tested. For variables with a normal distribution arithmetic means and standard deviations were calculated. Variables without a normal distribution were considered for log or square root transformation. Medians and interquartile ranges were calculated. Characteristics of the two time points were compared and, where appropriate, differences between the two studies were calculated and assessed for statistical significance using Chi-squared (categorical variables) and ANOVA (continuous variables) tests. Pearson's Chi-square and Phi coefficient and Pearson's product-moment correlation coefficient were calculated for categorical and continuous variables respectively.

Regarding ethnicity, small numbers of participants were of South Asian, East Asian, Latin American or Other descent. For statistical analysis these categories were combined into a single variable "Other" ethnicity, resulting in four ethnicity categories: White, Black African,

Black Caribbean and Other, allowing a closer examination of relationship between ethnicity and factors associated with dysglycaemia.

To assess risk factors associated with prediabetes and T2D, these two categories were combined into a single dependent variable labelled dysglycaemia, given evidence from the general population (Narayan et al., 2003) and in other HIV cohorts (Polsky et al., 2011, Capeau et al., 2012) that those with prediabetes are likely to progress to type 2 diabetes. For dietary analysis prediabetes and T2D were analysed separately as participants with T2D were more likely to have changed their dietary intake as a result of diagnosis, whereas those with prediabetes were largely diagnosed with this condition on entry to this study. For both 2005 and 2015 data univariate analysis of associations with dysglycaemia was performed using Chi-squared and ANOVA tests. Collinearity was tested between variables. For analysis of dietary intake, comparison between normoglycaemia, prediabetes and T2D was performed using ANOVA with Tukey's Honestly Significantly Different (HSD) test used to identify differences between groups. Additionally a Bonferroni adjustment was made to the alpha significance level. As there were three comparisons made, the alpha significance level used for comparison of dietary intake between groups was 0.017.

Binary logistic regression models were constructed for data from 2005 and 2015 to distinguish the independent contribution of factors to dysglycaemia. All variables demonstrated through univariate analysis to be significantly associated with dysglycaemia were considered for inclusion in the model. However, any pairs of variables with significant Pearson correlation were examined and only one variable of the pair was included in the model, chosen by clinical significance (Cohen, 1992). The backwards stepwise removal method was used, where variables lacking a statistically significant relationship were systematically removed (Menard, 2002). Odds ratios with confidence intervals were calculated.

Two logistic regression model options were considered. The first option pooled all HIV-related variables and compared these with general (non HIV-related) variables. The second option pooled all fixed variables and compared these with modifiable variables. The second option was chosen as information regarding modifiable factors was considered clinically relevant. Modifiable variables were defined as those amenable to lifestyle change, with or without added effect from medication, for example hepatic steatosis and triglycerides. Fixed variables were defined as historic or those that would not respond to lifestyle change, for example duration of HIV infection and age. Three models were constructed: fixed variables alone,

modifiable variables alone, and all variables together. The ability of each of the three models to predict dysglycaemia was measured using the area under receiver operator characteristic (ROC) curves (Alemayehu and Zou, 2012). ROC curves are most often used to calculate clinical thresholds when developing tests or markers for a disease. In this instance, the difference in proportions of the area under the curve (AUC) was used to determine which model best predicts dysglycaemia.

Receiver Operator Characteristic (ROC) curves were also used to investigate sensitivity and specificity for the various tools used to estimate disease risk, comparing how each disease risk equation correctly or incorrectly classified those at high risk of CVD or dysglycaemia. The overall strength of prediction of each equation was estimated using the AUC and its statistical significance. The number of cases of comorbid disease correctly identified by each prediction tool was also compared using Pearson's correlation.

2.6 Diet and Physical Activity Intervention

2.6.1 Rationale for Pilot Intervention Design

The aim the intervention presented in this thesis was to investigate the effect of individualised diet and exercise advice on markers of insulin resistance in PLWH at risk of developing T2D. Evidence that in PLWH diet or exercise change even when delivered with intensive support impacts weakly on insulin resistance, coupled with the uniquely diverse aetiology of dysglycaemia in PLWH, led to the decision that effectiveness must be explored prior to conducting a randomised controlled trial. This follows the guidelines recommended by the MRC for development of complex interventions (Craig et al., 2008). As previously described (Table 1.10) there have been six interventions in PLWH reporting the effects of diet or exercise on markers of insulin resistance. All six interventions were designed with highly intensive support, with daily or weekly sessions with dietitians or exercise instructors over three to 12 months. One trial provided all meals for the day. In two of the six studies markers of insulin resistance or HbA1c were reduced following the intervention whereas the other four studies showed no effect. Given the increasing prevalence of overweight and obesity in PLWH, the potential for lifestyle intervention to have a greater effect than in earlier interventions warranted investigation.

2.6.2 Choice of Intervention Structure

I based the intervention design on four large diabetes prevention trials (Table 1.8), with goals set for diet and physical activity change, and a target of 7% weight loss over six months (Knowler et al., 2002, Walker et al., 2010) (Figure 8). People living with HIV experience specific issues regarding diet, exercise and weight loss. These include the need to maintain lean body mass to support immune function (Wheeler et al., 1998), the pharmacokinetic importance of observing food-ARV interactions (Tseng et al., 2015) and consideration of metabolic issues (Table 1.2). Given these issues and the diversity of the cohort, an individualised advice approach was chosen. This was to be delivered by me, a dietitian specialising in HIV care, over a 6-month period with monthly review appointments. Markers of insulin resistance were measured at the start and end of the intervention together with a range of secondary outcome measures.

2.6.3 Diet, Physical Activity and Behaviour Change

For this study, in addition to the primary goal of reducing insulin resistance, I gave consideration to the prevalent metabolic health issues faced by PLWH including hypertension, dyslipidaemia and the risk of developing osteoporosis. The Mediterranean diet has a positive effect on dyslipidaemia and other health outcomes (Sofi et al., 2008). The DASH diet reduced hypertension (Appel et al., 1997). Both have been used to good effect in diabetes prevention trials (Martinez-Gonzalez et al., 2008, Liese et al., 2009). The two dietary approaches are described in Table 2.5 (Bach-Faig et al., 2011). For this intervention with the specific needs of PLWH in mind I chose to use a pragmatic combination of Mediterranean and DASH dietary approaches. Dietary and physical activity goals are described in Figure 8.

Table 2.5: A Comparison of the Mediterranean and DASH Diets

	Mediterranean	DASH
Carbohydrates	>50% carbohydrates from wholegrains	7-8 portions / day Sweets 2/week
Fats	Olive oil daily	Low fat overall 3 tablespoons oil/fat per day
Protein foods	↓ meats and poultry ↑ fish, pulses, nuts, seeds	↓ meat and poultry ↑ fish Nuts/seeds/pulses 5/week
Fruits and vegetables	Fruit 1-2, vegetables 3+ per day	8+ portions / day
Salt	No specific limit	No added salt
Dairy	2 portions low fat dairy / day	2 portions low fat dairy / day
Other	Red wine in moderation	

Source: A Duncan

Behaviour Change:

NICE guidelines recommend that when developing interventions specific behaviour change techniques should be used to support adherence and these must meet individual needs (NICE, 2014a). In complex interventions the function and process of the intervention should be standardised, not the components themselves in order to maximise effectiveness (Hawe et al., 2004). To date there is no published research regarding behaviour change in diet and physical activity interventions in PLWH. I therefore chose behaviour change techniques and supporting strategies listed in Tables 2.6-2.8 based on prevalent themes from the literature review presented in Table 1.11 on page 52.

Using the Theoretical Domain Framework to categorise these (Cane et al., 2012), I concluded that the principal areas requiring behaviour change support in lifestyle interventions are: goals; beliefs about consequences and outcomes; reinforcement and incentives; environmental context and resources; social influences and group norms; behavioural regulation and self-monitoring. Techniques to support change within these domains required a standardised delivery and support framework; I chose motivational interviewing and cognitive behavioural therapy, widely used in diabetes prevention and also in HIV transmission risk behaviour change interventions (Naar-King et al., 2012) (Reinhardt et al., 2012).

Figure 8: Intervention Participant Goals

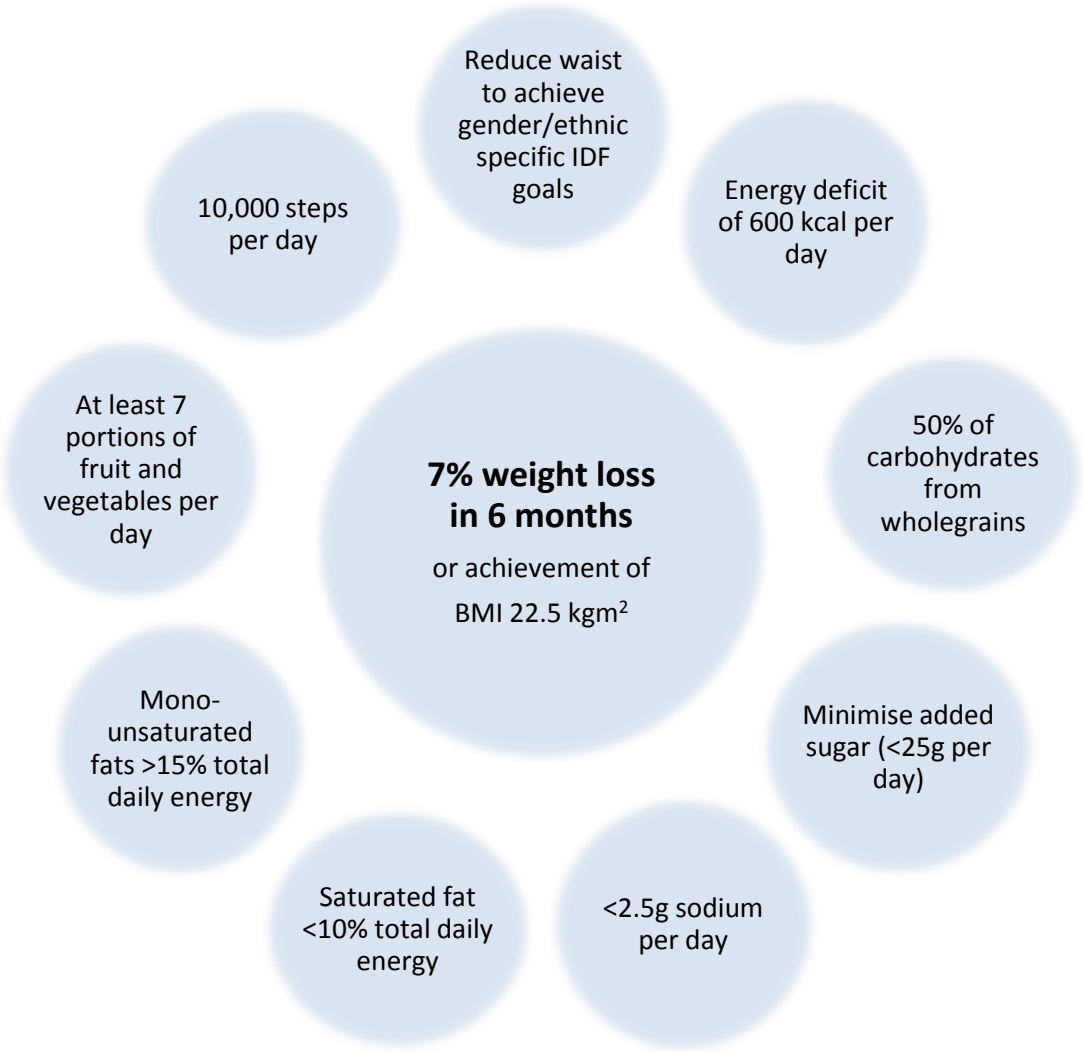


Table 2.6: Diet and Exercise – Individualisation of Intervention Components

	Standardised Process	Individualised Component	Refs
ENERGY	Daily deficit of 600 kcal / day based on estimated total energy expenditure	Estimate energy expenditure based on weight, age, gender and activity using modified Oxford equations	1
WEIGHT	Goal to achieve 7% weight loss in 6 months, or until BMI of 22.5 kg/m^2 achieved	If 7% weight loss would result in a BMI <22.5 kg/m^2, then target weight = BMI 22.5 kg/m^2	2
WAIST	Aim to ↓ waist size until IDF risk targets achieved: less than 94cm (♂), 90cm (Asian ♂), 80cm (♀)	Where achievement of waist target is unlikely in 6 months, negotiate achievable target, with a guideline of 7% reduction	3
FAT	Saturated fat to comprise <10%, and monounsaturates >15 % of total daily energy intake	Advice should reflect ethnicity, food habits, socioeconomic status, lifestyle patterns, access to food, cooking ability. Tailor advice to medical issues, e.g. raised LDL	4
CARBOHYDRATE	>50% of carbohydrate intake from wholegrains	As for fat. Individualise advice for any gastrointestinal symptoms	5
ADDED SUGARS	Restrict added sugar, sugar-sweetened drinks, biscuits, cakes, sweets	Discuss use of artificial sweeteners, diet drinks and alternatives to sweet foods	6
SODIUM	<6g salt daily (<2.5g sodium / day)	As for fat. Sodium restriction may be an agreed priority for those with hypertension	7
FRUIT & VEGETABLES	≥7 portions fruit and vegetables daily	As for fat. Cognisance of fruit and vegetables perceived as most expensive part of dietary change	7
FISH	2 portions fish/week, one of which should be oily	As for fat. May be a priority for those a higher CVD risk	8
STEPS PER DAY	10,000 steps/day, building gradually by 1,000 steps/day until goal achieved or exceeded	Methods of achieving 10,000 steps/day based on individual's current lifestyle, ability, motivation, and external factors	9,10
PHYSICAL ACTIVITY	30 minutes moderate physical activity 3/week, building incrementally	Consider accumulating 30 minutes in shorter blocks across the day. Type of activity to suit individual	11
ALCOHOL	No standard goal for alcohol	Reduce alcohol to effect overall reduction energy intake where appropriate	12
EATING PATTERNS	Eat three times per day, spread across the day. Encourage healthy snacks	Advice should reflect food habits, lifestyle, access to food, medical issues, food-drug interactions	13

References: 1 - (Henry, 2005); 2 - (Tuomilehto et al., 2001); 3- (Alberti et al., 2006); 4 - (Ericson et al., 2015); 5- (Aune et al., 2013); 6- (Gardner et al., 2012); 7- (Liese et al., 2009); 8 - (Stradling et al., 2012); 9 - (Yates et al., 2009); 10 - (Tudor-Locke et al., 2011); 11 - (Knowler et al., 2002); 12 - (Knott et al., 2015); 13 - (Tseng et al., 2015)

Source: A Duncan

Table 2.7: Behaviour Change Techniques – Individualisation of Intervention Components

	Standardised Process	Individualised Component	Refs
REINFORCEMENT	Reminder & motivational text messages	The content of the text message will be individualised, or alternatives used where participant declines text messages, e.g. email	1
COGNITIVE BEHAVIOURAL THERAPY (CBT)	Identify critical behaviours or unhelpful thinking, evaluate frequency and intensity, reconceptualise to aid understanding, facilitate skills to replace behaviour, set goals, assess progress	Need for CBT will be identified on an individualised basis. Reconceptualisation, facilitation of skills and goal setting all require an individualised approach	3
MOTIVATIONAL INTERVIEWING	Elicit change talk, evoke motivation from participant, agree goals, positive encouragement, foster autonomy	Use at every contact but individualise to reflect participant's abilities, ethnicity, customs, lifestyle	4
CONSEQUENCES AND OUTCOMES	Day 1: health implications of developing T2D will be discussed	Revisit across the 6 months as appropriate, including health outcomes other than T2D	2
LEARNING FROM PERCEIVED FAILURE	Participant's perception of an experience as a failure acknowledged by dietitian, then position this as a learning experience	Technique used where appropriate, if participant perceives failure	4
SOCIAL INFLUENCES AND GROUP NORMS	Support from others will be discussed with all participants	Support may be from family, friends, peers, or colleagues, individualised to participant's situation. In cases of isolation, greater support from study dietitian or from charities or agencies will be discussed	5
REWARD FOR ACHIEVEMENT	Reward for achievement encouraged, with the caveat that food or alcohol should not be used as a reward	Individual to identify own reward	5
References: 1 - (NICE, 2014a); 2 - (Baker et al., 2011); 3 - (Tuah et al., 2011); 4 - (Martins and McNeil, 2009); 5 - (Paulweber et al., 2010)			

Source: A Duncan

Table 2.8: Participant Information and Resources – Individualisation of Intervention Components

	Standardised Process	Individualised Component	Refs
PEDOMETER	CW-600 digi-walker given to all participants at first visit, with instructions for use and how to record daily number of steps in diary	Smart phone can be used as an alternative, with discussion that when phone not in pocket steps will not be recorded	1,2
DIETARY ADVICE BOOKLETS	National Dietary Resources (NDR-UK) "Weight Loss You Can See" booklet given to all participants at first visit	African and Caribbean inserts	3
DAILY DIARY	Participants encouraged to record food and mood, daily record of number of steps achieved, challenges, successes, and any questions or issues to raise at next visit. Given at first visit	To be completed by all participants at a level decided by the individual	3
DIET RESOURCE SHEETS	Summary of standardised dietary goals for the interventions with suggestions how to achieve these, given at first visit	Delete any inappropriate items in booklet e.g. allergenic foods	3
PHYSICAL ACTIVITY RESOURCES	British Heart Foundation (BHF) Get Active Stay Active booklet, given to all participants at second visit	Additional resources on an individual basis, e.g. African and Caribbean Diabetes UK booklet	3
FOOD SAMPLES	At second visit discuss food samples: low salt, wholegrains, low fat, and encourage to take samples away to try	The participant to choose which items preferred	4
FOOD LABELS	Resource sheet explaining how to understand food labels given at second visit	For all participants. Extra resources available for individuals who require further explanation	3
MRC FOOD DIARY	5 day diary using photographs to aid estimation of portion size. Given prior to first and last visits	For all participants	5
References: 1 - (Yates et al., 2009); 2 - (Tudor-Locke et al., 2011); 3 - (Baker et al., 2011); 4 - (Moore et al., 2009); 5 - (Medical Research Council, 2016)			

Source: A Duncan

2.6.4 Methodology for Measuring Primary Outcome

The primary outcome for the intervention was the change from baseline at 6 months for markers of insulin resistance, specifically glucose incremental area under the curve. A range of methods are used in clinical research for measuring glycaemic status, insulin sensitivity / resistance, and glucose disposal; this is summarised in Table 2.9. Of these methods, the three I considered for measuring the primary outcome in this study were the hyperinsulinaemic-euglycaemic clamp (HIEC), the oral glucose tolerance test (OGTT), and the frequently sampled liquid meal tolerance test (FSLMTT). My rationale for selecting the FSLMTT is outlined below.

The HIEC is considered to be the gold standard for measuring insulin sensitivity/resistance. It has been used extensively in research with HIV-positive participants (Neye et al., 2006, Taylor et al., 2010, Nguyen et al., 2014, Moreno-Perez et al., 2013). However the HIEC is time-consuming, labour-intensive and expensive to implement, requiring a trained and experienced operator. Additionally, due to the HIEC being based on intravenous stimuli it may not reflect insulin and glucose dynamics under normal physiological conditions, for example those occurring after normal meals (Roden, 2007).

The OGTT is a well-established test requiring considerably less training, experience and resources than the HIEC. It has been used extensively in HIV patients (Gianotti et al., 2011). The use of frequent sampling points over a 120 or 180 minute time course allows for more sophisticated modelling of insulin and glucose dynamics and estimation of insulin sensitivity (Roden, 2007).

More recently meal tolerance tests have been favoured over the OGTT because mixed nutrient stimuli more closely mimic usual physiological eating. I selected the FSLMTT as the method for measuring the primary outcome as it would provide the most detailed level of data with a reasonable use of resources and with only a modest burden for participants (Roden, 2007). The use of a mixed-nutrient liquid meal would allow examination of the effect of incretins.

Table 2.9: Methods for Measuring Insulin and Glucose Dynamics

Method	Description	Notes	Ref
Fasting glucose and insulin	Single phlebotomy after an overnight fast	Least participant burden. Simple indices e.g. HOMA	(Matthews et al., 1985)
HbA1c	Surrogate for medium-term glycaemic control that does not require fasting	More expensive than glucose. May be less accurate in HIV patients	(Eckhardt et al., 2012)
Oral Glucose Tolerance Test (OGTT)	75g glucose (fasting), up to 4 samples over 120 mins, Clinically glucose only but adding insulin allows modelling	Simple physiological test used to diagnose IGT and diabetes.	(American Diabetes Association, 2014)
Meal tolerance test	Measured meal eaten in fasting state, glucose and insulin at several time points 120-180 minutes afterwards	Demanding for investigators to ensure consistency, most physiologically relevant, lower GI than OGTT, evaluates incretins	(Lefebvre and Luyckx, 1976)
Frequently Sampled OGTT (FSOGTT)	Extended version of the OGTT with insulin and glucose measured at up to 11 time points over 120-180 minutes	Moderately intensive. More physiologically representative than the FSIGTT	(Penesova and Radikova, 2004)
Frequently Sampled Liquid Meal Tolerance Test (FSLMTT)	Insulin and glucose are sampled frequently over 120-180 mins following a mixed-nutrient liquid meal (fasting)	Moderately intensive. Readily reproducible for investigators. Evaluates incretins	(Maki et al., 2011)
Frequently sampled intravenous glucose tolerance test (FSIGTT)	Over 180 minutes following an IV bolus of glucose in the fasting state frequent insulin and glucose samples are modelled to produce an insulin sensitivity index	Moderately intensive. Tends to be inaccurate in those with diabetes who secrete little insulin and have insulin resistance	(Finegood et al., 1990)
Insulin suppression test (IST)	Fasting, IV octreotide suppresses endogenous insulin secretion, IV insulin & glucose given, samples at 150-180 mins determine muscle insulin sensitivity	Slightly less intensive than the HIEC. Does not reflect hepatic insulin sensitivity or action of incretins	(Pei et al., 1994)
Insulin Tolerance Test (ITT)	A standard bolus of insulin is given IV in the fasting state. Drop in glucose at 8 time points over 30 minutes gives measure of insulin sensitivity	Hypoglycaemia can occur requiring monitoring / IV glucose. Does not differentiate peripheral vs hepatic insulin sensitivity	(Hirst et al., 1993)
Hyper-insulinaemic-euglycaemic clamp (HIEC)	Fasting, insulin infused IV to suppress gluconeogenesis. Glucose IV to achieve steady state at normal blood glucose	Considered gold standard. Expensive and labour intensive. Potential burden on participant	(DeFronzo et al., 1979)

Source: Review by A Duncan

Various models of FSLMTT have been used (Table 2.10), for example using carbohydrate doses ranging from 33-80g, 15-18g protein, and 6-12g fat in a 150-500ml dose. I developed a protocol for the FSLMTT using a readily-available mixed nutrient drink, Fortisip Compact™. This product is produced under strict conditions resulting in a reliably consistent delivery of nutrients. A dose of 200g weighed using electronic scales provided 60g carbohydrate, 19g protein and 18g fat. Other studies used time points ranging from 0-120 to 0-240 minutes. For this study 0-180 minutes was chosen in order to characterise any delayed response to a meal challenge in HIV patients. Consultation with a patient-public involvement group had led to the decision to limit research visits to a maximum of 4 hours, therefore extending the test to 4 hours post meal would breach this timescale, and potentially add limited extra data. I developed a standard operating procedure for the FSLMTT (Appendix 5).

2.6.5 Frequently Sampled Liquid Meal Tolerance Test Procedure

In the 24 hours prior to the FSLMTT participants were instructed to refrain from vigorous exercise, smoking and alcohol, and to eat three standard meals containing carbohydrates. Fasting was defined as nothing to eat and only water to drink from 10 hours prior to attending. In practice all FSLMTTs commenced between 8 and 10am to suit the participant and fasting commenced between 10pm and midnight accordingly. In order to prevent risk of dehydration and aid ease of phlebotomy participants were encouraged to drink 500-1000ml water prior to leaving home to attend the FSLMTT appointment. On the morning of the FSLMTT a qualified research nurse inserted a BD Nexiva™ Dual Port 20 Gauge 25mm cannula into the participant's antecubital fossa on the non-dominant arm using intradermal lignocaine (1%) to anaesthetise the skin, employing standard aseptic techniques. After a period of 10 minutes allowing the participant to relax, fasting samples for glucose, insulin, lipids and HbA1c were taken from the cannula, as outlined in Table 2.11. A zero sample was taken 10 minutes later followed immediately by the participant being asked to consume the liquid meal. Participants chose to consume the liquid meal either at room temperature or chilled from the refrigerator. The choice was noted and repeated at the post-intervention visit as temperature can affect rate of gastric emptying (Mishima et al., 2009). Participants were informed that they should consume the entire 200g dose in steady sips and were timed using an electronic stopwatch to ensure a maximum time of 120 seconds was not exceeded.

Table 2.10: Frequently Sampled Liquid Meal Tests – Models Used

Study and Reference	Preparation	Liquid Meal Used	Phlebotomy	Notes
(Bacha et al., 2013) USA, adolescents with T2D	12 hour overnight fast, insulin stopped 6 hours before test	237ml dose of Boost-HP™ (Nestle): 33g CHO, 15g protein, 6g fat	0, 15, 30, 60, 90, 120 minutes	Test used to develop indices for insulin secretion
(Besser et al., 2013) Sweden, children with T1D	Water only after 10pm, no smoking, no short acting insulin	Sustacal™ (Nestle) - 1kcal/ml drink, 6ml/kg, max dose of 360ml. 360ml provides 52g CHO, 15g protein, 10g fat	0, 30, 60, 90, 120, 150	Author describes this method as "routine clinical practice"
(Diabetes Prevention Trial Group, 2002) USA & Canada, relatives of T1D with high islet cell antibodies	Overnight fast (nil else mentioned in methods)	Sustacal™ or Boost-HP™, for either max dose of 360ml	0, 15, 30, 60, 90, 120	One of several methods used in this trial
(Maki et al., 2009) USA, adults with T2D	48 hours before test consume >150g CHO/d. Avoid exercise. Confirm these 2 before fasting for 10 hours	500g chocolate Ensure™ (1kcal/ml), consume within 10 minutes. Provides 80g CHO, 18g protein, 12g fat	0, 30, 60, 90, 120, 150, 180, 210, 240	Author used tests to develop indices for secretion and sensitivity
(Maki et al., 2010) USA, adults with normal glucose IFG and T2D	48 hours before test consume >150g CHO/d, avoid exercise, fast for 10 hours	500g chocolate Ensure™ (1kcal/ml), consume within 10 minutes. Provides 80g CHO, 18g protein, 12g fat	0, 30, 60, 90, 120, 150, 180, 210, 240	Author describes repeatability of indices for secretion and sensitivity
(Maki et al., 2011) USA, adults with increased waist but not T2D	Overnight fast (nil else mentioned)	500g Ensure™ (1kcal/ml), consume within 10 minutes. Provides 80g CHO, 18g protein, 12g fat	0, 30, 60, 90, 120	Uses this test in validation of LMTT against IVGTT
Note: CHO - carbohydrate				

Source: Review by A Duncan

Over the next three hours blood was taken at 5, 10, 15, 30, 60, 90, 120, 150 and 180 minutes. A total of 86ml of blood was taken during the test. Saline (0.9%) was flushed before and after each blood draw to maintain patency of the cannula and lines. In order to prevent dilution of samples with saline, 2ml blood was discarded prior to obtaining each sample. An additional blood sample was drawn and together with a urine sample transferred for processing and long-term storage at -80^{o}C in the KCL Infectious Diseases BioBank at Guy's Hospital. The intention for these samples is to investigate gene expression and metabolomics. This proposed study is not part of the research presented in this thesis.

Table 2.11: Sampling Schedule for the Pre and Post Intervention Visits

	Time in Minutes										
	-10	**0**	**5**	**10**	**15**	**30**	**60**	**90**	**120**	**150**	**180**
Glucose (2ml fluoride oxalate)	x	x	x	x	x	x	x	x	x	x	x
Insulin (2ml clotted serum)	x	x	x	x	x	x	x	x	x	x	x
Lipids (2ml clotted serum)	x										
HbA1c (2ml EDTA)	x										
Incretins (2ml EDTA + DPPIV inhibitor)		x				x	x		x		
Sample for future DNA analysis (EDTA)	x										
Urine sample for future metabolomics analysis	x										

Source: A Duncan

All specimens were labelled using a unique study identification code with no identifiable information recorded on samples. The code used was in the format: STOP123AB1. This referred to: STOP – The STOP Diabetes in HIV study; 123 – Participant study number; AB – Participant initials; 1 – Visit number. In addition specimens were labelled with the analyte and time point of collection in minutes, for example GLU 0, INS 90. Vacutainer tubes for all samples other than insulin were chilled on ice prior to drawing samples. Samples were processed (Table 2.12) prior to placing in 2 cryotubes (primary and duplicate sample) and were racked in 10 x 10 cryogenic storage boxes in a -80^{o}C freezer. Finally, once all participants completed the intervention primary samples were couriered to the King's Lab for analysis, remaining frozen during transit using dry ice.

Table 2.12: Processing Schedule for Intervention Blood Samples

Analyte	Sampling Tube	Preparation	Volume
Glucose	Fluoride oxalate (grey)	Stored on ice and centrifuged within 15 minutes at 2500 rpm at 4°C	2ml blood, aliquot serum into 2 cryovials for freezing
Insulin	Plain clotted (gold)	Room temperature for 30 minutes. Centrifuged at 2500 rpm at 4°C	2ml blood, aliquot serum into 2 cryovials for freezing
Incretins	EDTA (purple) with 100µl DPPIV inhibitor added	Stored on ice and centrifuged within 2 minutes at 2500 rpm at 4°C	2ml blood, aliquot serum into 2 cryovials for freezing
Lipids	Plain clotted (gold)	No preparation: sent directly to Guys lab	2ml blood
HbA1c	EDTA (purple)	No preparation: sent directly to Guys lab	2ml blood
Sample for lymphocyte DNA	EDTA (purple)	Courier transferred at room temperature to the BioBank for processing	2 x7ml vacutainers
Notes: 2500 rpm in the centrifuge used is equivalent to 559 times gravity EDTA: Ethylene Diamine Tetra-acetic Acid			

Source: A Duncan

2.6.6 Modelling Glucose and Insulin Dynamics

Glucose and insulin results from the tests described in Table 2.9 can be modelled to estimate insulin sensitivity, insulin resistance, β-cell function and glucose clearance rates. Several models have been developed and tested in various patient groups and those commonly used are described in Table 2.13. For this study, I chose a range of indices of insulin sensitivity, resistance and glucose clearance rates.

HOMA and QUICKI have been used extensively in studies of HIV patients and have been validated for use within people of Black African origin (Ntyintyane et al., 2010). However, both use simple formulae based on fasting insulin and glucose only. The McAuley Index formula uses fasting triglycerides in addition to insulin; I selected this index as triglyceride levels can be high in PLWH (Alencastro et al., 2011). Finally, the oral glucose insulin sensitivity index (OGIS) was chosen to estimate glucose clearance as all variables required for the complex equation were available from the FSLMTT.

Table 2.13: Glucose and Insulin Modelling Indices

Tool	Description	Factors Used in Formula	Correlation with HIEC in IFG	Use in HIV Cohorts
HOMA (Matthews et al., 1985)	Simple insulin resistance index	Fasting glucose and insulin	0.56	Widespread and validated
QUICKI (Katz et al., 2000)	Simple insulin sensitivity index	Fasting glucose and insulin	0.51	Widespread and validated
Matsuda (Matsuda and DeFronzo, 1999)	Modelled insulin sensitivity index	Insulin and glucose at 0 and 120 minutes	0.66	Some use
Avignon (Avignon et al., 1999)	Modelled insulin sensitivity index	Insulin and glucose at 0 and 120 minutes, and body mass	0.83	Not reported in research published to date
McAuley (McAuley et al., 2001)	Insulin resistance prediction	Fasting insulin and triglycerides	0.63	Not reported in research published to date
Stumvoll (Stumvoll et al., 2000)	Insulin sensitivity prediction	Fasting insulin and 120 minute insulin and gluose, plus age, gender and BMI	0.62	Not reported in research published to date
Cederholm (Cederholm and Wibell, 1990)	Surrogate of insulin sensitivity and glucose disposal rate	Fasting glucose and insulin over time following a glucose dose plus body mass	0.63	Not reported in research published to date
OGIS (Mari et al., 2001)	Insulin sensitivity prediction and glucose	Glucose clearance calculated using insulin and glucose at 0,60,120 plus body surface area	0.65	Not reported in research published to date

- Abbreviations: HIEC – Hyperinsulinaemic-euglycaemic clamp; IFG – Impaired fasting glucose; HOMA – Homoeostatic model of assessment; QUICKI – Quantitative insulin sensitivity index; OGIS – Oral glucose insulin sensitivity.
- Source of HIEC correlations: (Gutch et al., 2015)
- Date of search for use of indices in HIV cohorts: 4/4/16

Source: Review by A Duncan

2.6.7 Power Calculation, Intervention

Powering a Hypothetical Randomised Controlled Trial:

In the PREPARE study, an RCT carried out in an HIV negative UK population (Yates et al., 2009), investigators measured the effect on insulin resistance of a 6 month course of advice to increase physical activity. Measured by an OGTT, they observed a 0.8 mmol/l drop in 2-hour post-load glucose when comparing the intervention and control arms. Assuming this same effect size of a difference of 0.8 mmol/l post-load plasma glucose between an intervention and control arm in a hypothetical RCT investigating HIV patients at risk of developing diabetes, 25 participants would need to complete the study per group in order to detect this difference with a power of 80% using a significance level of 0.05.

Powering The Intervention Presented in this Thesis:

As previously described, a single intervention arm was chosen for this pilot study investigating effectiveness rather than an RCT. Planning to follow up at least 30 participants to completion of the 6 month intervention, it was estimated as many as 46 would need to be recruited to achieve this. The drop-out rates for lifestyle intervention studies in HIV patients are potentially as high as one in three (Fitch et al., 2012) as lifestyle change may be more difficult to maintain in this cohort (Petroczi et al., 2010). It was estimated that recruiting 46 patients with a 33% drop-out rate would result in 30 participants completing.

It was calculated that with 30 participants followed up it would be possible to obtain an informative estimate of the primary outcome: standard deviation (SD) of the change in markers of insulin resistance, specifically incremental area under the curve for glucose over the three-hour FSLMTT. A 95% confidence interval for the SD would range from 0.775 to 1.32 times higher than the obtained estimate of the SD (Vickers, 2003). As it was estimated that 30 participants followed up to completion would be a sufficient number to estimate the SD for other continuous outcomes collected (Browne, 1995), any subsequent sample size calculations for future investigations would be able to use these SDs.

2.6.8 Inclusion and Exclusion Criteria, Intervention

Participants were eligible for participation in the intervention study as follows:

- HIV positive adults (aged ≥18 years old)
- Stable on their current HAART regimen for at least the last 6 months (stable is defined as: tolerating their therapy well without a wish or need for change)
- Unlikely to need to change their ARVs within the next 6 months
- Have impaired fasting glucose (5.6 – 6.9 mmol/l inclusive)
- Able to give informed consent
- Willing and able to participate in a diet and exercise programme
- Able to attend monthly appointments for 6 months
- In the opinion of the investigator unlikely to have any planned events within the scheduled 6 months that would prevent adherence to a lifestyle change programme
- Competent in English language

Participants were ineligible as follows:

- Have a clinical diagnosis of type 1 or type 2 diabetes
- Have a fasting glucose indicative of diabetes (≥7.0 mmol /l)
- Have a random glucose indicative of diabetes (≥11.1 mmol/l)
- Pregnant, planning for a pregnancy, or lactating
- Naive to antiretroviral therapy
- Have medical problems that may interfere with patient safety
- Have a current medical condition that makes dietary change or exercise inadvisable
- Are fitted with an artificial cardiac pacemaker device
- Have liver impairment suggested by liver function tests (ALT) within the last year elevated ≥2.5 times above the upper level of the laboratory reference range
- Have hepatitis B or C co-infection
- Use medicines that might interfere with glucose homeostasis measures, e.g. corticosteroids, anabolic steroids, testosterone or diabetes medications
- Currently serving a custodial sentence

Only those participants stable on ARVs and unlikely to change regimens during the 6-month intervention period were eligible, as metabolic changes as a direct result of initiating or changing ARVs could potentially confound any intervention effect (Busti et al., 2008).

2.6.9 Data Collection Methods, Intervention

The following data collection methods were used in the pilot intervention study:

Demographic, Social and Socioeconomic Data:

Ethnicity and gender data were recorded as described for the phenotype study. Age was recorded at baseline of the intervention.

Anthropometry:

At every visit height and weight were measured using standardised calibrated electronic equipment, and BMI was calculated and categorised as: underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥30.0 kg/m^2). Waist and hip circumferences were measured using a non-stretch tape measure and categorised using ethnic and gender-specific International Diabetes Federation (IDF) criteria (Alberti et al., 2006); these criteria were also used to define metabolic syndrome as described in Table 2.4. Waist was defined as the midpoint between the lowest and rib and the supra-iliac crest. The hip measurement was taken at the largest circumference around the buttocks with the tape measure held horizontal above the supra-pubic bone. Clothing that might obstruct the measurements were moved from the waist and hip area. The participant was then asked to stand upright with arms relaxed at the side, feet evenly spread apart at approximately shoulder width, and body weight evenly distributed.

Body Composition:

Bioelectrical impedance analysis (BIA) was performed at baseline and post-intervention using a Quadscan 4000 multifrequency bioelectrical impedance analyser in order to estimate fat and lean body mass. The device has been validated in PLWH of different ethnicities and in those with or without lipodystrophy (Forrester et al., 2008). Use of this device is contraindicated if the participant has an indwelling pacemaker device or knows or suspects pregnancy. Participants were invited to lie on an examination couch for 5 minutes while data was inputted into the device. Four single-use self-adhesive electrode pads were attached, 2 each to the right wrist and ankle, and then connected to the Quadscan by attaching 4 leads. Dry lean weight, total fat mass, total body water and impedance were recorded.

Socioeconomic Status:

Socioeconomic status was calculated at baseline using the same methods described in the phenotype study in Section 2.5.4, namely NS-SEC, the MacArthur scale, an assessment of financial struggle and Attainment of higher education was also ascertained.

Social and Lifestyle Factors:

A range of lifestyle factors was recorded in order to characterise the variables needed for CVD and diabetes risk calculations at baseline and post-intervention (Hippisley-Cox et al., 2009, Hippisley-Cox et al., 2008, Gray et al., 2010). Usual consumption of portions of fruits and vegetables per day was recorded as well as hours per week of physical activity defined as exertion greater than usual walking speed. Smoking status was categorised as current, never, or ex-smoker, with number of cigarettes recorded. Social isolation was defined as a state in which the individual lacks a sense of belonging socially, lacks engagement with others, has a minimal number of social contacts and they are deficient in fulfilling and quality relationships (Nicholson, 2009). Presence of social isolation was recorded as specific expression by the participant of one or more of these factors at baseline, midpoint and post-intervention.

Quality of Life:

A range of HIV-specific quality of life assessment tools and questionnaires has been produced. The HIV Medical Outcomes Study (MOS-HIV) 35-item instrument questionnaire (Wu et al., 1997) and the HIV/AIDS Targeted Quality of Life (HAT-QoL) questionnaire have been used most extensively in clinical trials with PLWH (Clayson et al., 2006). The HAT-QoL questionnaire was chosen to assess the impact of the 6-month intervention on the participant's quality of life as it has been demonstrated to reflect a wide range of aspects of physical and mental health in those on HAART (Holmes and Shea, 1999). The questionnaire was completed by participants at baseline and post-intervention. It has nine sections with between 2 and 5 questions in each section. Analysis provides a percentage score in the following categories: satisfaction with life, health worries, financial security, issues around HIV medications, mastery of living with HIV, HIV disclosure issues, relationship with healthcare providers and sexual function, as well as a total quality of life score, also expressed as a percentage.

Dietary Intake, Food Habits and Access to Food:

Within research studies dietary intake is a challenging variable to measure, with a high potential for error when analysed (MacIntyre, 2009). Irrespective of method used to record and analyse dietary intake, underreporting occurs resulting in systematic bias (Freedman et al., 2006). A number of dietary assessment tools were considered for evaluation of intake. Dietary recall is not routinely used in research studies as resulting macro and micronutrient analysis is inaccurate (Bingham et al., 1994). Diet diaries completed prospectively by participants over a varying number of days reflect complete dietary intake as opposed to usual intake, producing a more accurate analysis as the number of days increases (Nelson et al., 1989). Participant enthusiasm and accuracy of recording decreases as number of days of recording increases. Accuracy is increased by use of weighing scales for diaries of a limited number of days (Livingstone et al., 1992). Additionally, in HIV positive participants, food frequency questionnaires validated in the general population were found to underestimate micronutrient intake compared to diet diaries (Hendricks et al., 2005).

Metabolic biomarkers can be used to assess dietary compliance with specific guidelines, for example serum linoleate, oleate and palmitate to correlate olive oil intake and urine sodium and potassium from 24-hour collections to correlate salt and fruit and vegetable intake respectively (Ismail et al., 2013).

For this study I considered the accuracy of calculating macronutrient intake a priority. Dietary intake was measured using the MRC Human Nutrition Unit 5-day diary at baseline and post-intervention. Participants were instructed to include at least one weekend day within their 5-day diary as variation between weekdays and weekend days can be significant (Thane, 2006). Twenty-four hour recall using the triple-pass method (MacIntyre, 2009) was used at monthly review meetings on days 30, 60, 90, 120 and 150 to monitor achievement of dietary goals but not for full analysis of intake. The MRC diary contains colour photographs and household measures of a wide variety of foods to aid recording of portion size (Medical Research Council, 2015). To improve accuracy diaries were reviewed with participants to clarify brands, portion sizes, food preparation methods and condiment use (Cantwell et al., 2006). Nutritional analysis of 5-day diaries was conducted using Nutritics™ dietary analysis software.

Wholegrains include whole wheat, wholemeal flour, wheat flakes, bulgar wheat, whole and rolled oats, oatmeal, oat flakes, oat flour, brown rice, wholemeal pasta, wholemeal rye and rye

flour, whole barley and popcorn. Dietary analysis of wholegrain intake can be challenging, secondary to coding of foods contained in analysis software and databases (Thane et al., 2007). For this study any foods containing ≥10% whole-grain content were defined as wholegrain in order not to exclude the contribution to whole-grain intake from porridge. Unlike other breakfast cereals consumed whole, porridge is coded as being made up with milk or water, and is estimated to have an 11% wholegrain content (Thane et al., 2007). Cornmeals consumed as staple foods in African diets were included as wholegrains only if product labelling indicated they had not been de-hulled, de-branned and de-germed. Foods containing high amounts of bran, but being deficient in endosperm or germ were not defined as wholegrains.

Physical Activity:

Physical activity was recorded at baseline and post-intervention using the International Physical Activity Questionnaire (IPAQ) widely used in clinical trials and validated in many populations (Craig et al., 2003). Activity was calculated as mean minutes per day sedentary time, walking, moderate metabolic equivalent of task (METs), intense METs and total mean MET minutes per day. At baseline participants were issued with a Yamax CW-600 digi-walker™ pedometer and instructed to record the number of steps walked each day on monthly record sheets for the entire intervention (Corder et al., 2007). Other physical activity was recalled at monthly visits on days 30, 60, 90, 120 and 150.

Gastrointestinal Habits and Symptoms:

Participants completed a functional bowel habits and symptoms questionnaire (Appendix 7.6) at baseline and post-intervention. Participants were asked to describe the severity of a range of gastrointestinal symptoms and complete the Bristol Stool Form chart. This questionnaire was developed by the gastroenterology group of the British Dietetic Association and is currently being validated. Each question is scored from 0-3, with no symptoms scoring 0, and severe symptoms scoring 3.

Medical Information:

All relevant current and historic medical information was recorded, including an exhaustive medication and supplement history. Relevant medical information included any condition that might affect diet or physical activity, comorbid conditions, and mental health issues. Blood pressure was measured and hypertension defined as described in the phenotype study (Abbott

et al., 1994). Co-morbidities checked were: cardiovascular disease including myocardial infarction, stroke or transient ischaemic attack, chronic kidney disease, polycystic ovary syndrome, osteopaenia or osteoporosis and hepatitis B or C. Although infectious hepatitis was an exclusion criteria for this study those successfully cleared of hepatitis C were categorised as negative. A history of gestational diabetes was also recorded.

HIV Parameters:

A full history of HIV-related factors was recorded, including known duration of HIV infection measured from the date of the first positive HIV antibody test, and duration of ARV therapy from the date of first use of any ARV. Exposure to ARVs associated with insulin resistance was defined as current or historic treatment with AZT (zidovudine), ddI (didanosine), ddC (zalcitabine), d4T (stavudine), Indinavir, or high-dose Ritonavir (De Wit et al., 2008), (Rasmussen et al., 2012) (Hadigan and Kattakuzhy, 2014). Weight change following initiation of ARVs and CD4 nadir were corroborated where possible from medical notes. CD4 count and HIV viral load were measured at baseline and post-intervention using routine clinical measures. HIV suppression was defined as current HIV viral load being undetectable (<50 copies per ml). Lipodystrophy syndrome was defined as current or historic by participant recall or physician diagnosis from the medical notes, and date of onset was recorded.

Marker of Frailty:

Handgrip strength (Norman et al., 2011) and the five-times sit-to-stand test (Richert et al., 2014) have both been validated as markers of frailty in PLWH (Kooij et al., 2016). Handgrip strength was chosen for this study as the sit-to-stand test is not validated in longitudinal investigations. At baseline and post-intervention participants were asked to perform handgrip using a dynamometer, twice with each hand. The mean handgrip strength was recorded.

2.6.10 Laboratory Analysis

Lipids and HbA1c

Dyslipidaemia was defined as in the phenotype study. Lipid fractions and additionally HbA1c were measured in the fasting state at baseline and post-intervention. Venous blood samples (2ml) were taken into EDTA tubes and immediately transferred for processing and analysis to the clinical laboratory at St. Thomas' Hospital.

Insulin, Glucose and Incretin Hormones

Sample analysis was performed at King's Lab in Denmark Hill, London:

Insulin:

The Siemens Advia Centaur assay was used to assess insulin levels (El Kenz and Bergmann, 2004). This is a two-site sandwich immunoassay using direct chemiluminometric technology. Samples were incubated with two monoclonal mouse anti-insulin antibodies. Insulin forms a sandwich between these two antibodies. Following incubation a magnetic field was applied holding the solid phase at the site of the reaction cuvette. After washing the cuvette was then moved to the luminometer and base reagent added to enhance the light reaction. Light intensity was measured immediately and converted to relative light units. Light units are directly proportional to insulin concentration.

Glucose:

Glucose was analysed using the Plasma Glucose Advia 2400 assay utilising the glucose oxidase method (Westwood et al., 1986).

Incretins:

GLP-1 is comprised of 37 amino acid residues and is mainly secreted in the form of GLP-1(7-36) amide in response to food intake. GIP circulates as a biologically active 42-amino acid peptide. Samples were degraded into their inactive form after cleavage by dipeptidyl peptidase-4 inhibitor added to the EDTA vacutainers. This assay is a Sandwich ELISA based on the total number of molecules from samples adhering to the wells of a microtiter plate coated by a pre-titred amount of anti- GLP-1 and anti- GIP polyclonal antibodies. Enzyme activity was measured spectrophotometrically, directly proportional to the amount of captured incretin. Incretin calibration curves were calculated and active incretin concentrations in the samples were interpolated (Tominaga et al., 1996).

2.6.11 Scheduling

The schedule for the 6-month intervention is described in Table 2.14. There were three principal visits scheduled. Day 1 and Day 180 marked baseline and post-intervention respectively, when the participant attended fasting and full data collection occurred including the FSLMTT to measure the primary endpoint. These visits were estimated to need approximately 4 hours to complete data collection.

An intervention mid-point visit was scheduled on Day 90. At this visit estimated to be of 1-hour duration, the participant attended fasting for a single phlebotomy and routine data collection. The rationale for collecting fasting insulin, glucose, lipids and HbA1c at this mid-point was to yield data for any participants who dropped out between months 3 and 6.

It was not possible within the protocol to have others collect or analyse data. In order to minimise bias, as far as possible I delayed analysis of results until the final participant exited, whilst at the same time being able to provide motivational feedback to individual participants on their progress over the intervention. I was aware of, and participants were informed about and motivated by their anthropometry, BIA results, fasting glucose and lipids at baseline and midpoint, handgrip strength and blood pressure. Analysis of the remainder of results was delayed until the final participant exited the intervention. This included analysis of blood glucose and insulin samples collected from the FSLMTT, analysis of all questionnaires, calculation of CVD and T2D risk and statistical analyses.

2.6.12 Outcome Measures

Recruitment rate was defined as the proportion of eligible patients who consented to participate at intervention baseline. The attrition rate was defined as discontinuation or loss to follow-up of participants over the 6 months. Attendance at the monthly appointments and completion of food diaries will be used as indicators of participation and study compliance. Achievement of each of the 10 goals for the intervention described in Figure 8 was recorded and aggregated into a score. Achievement of 6-10 goals was considered high, 3-5 goals moderate, and 2 or fewer low.

Table 2.14: Intervention Schedule – Procedures and Data Collection

Visit type	Screen	Day 1	Day 14	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180
Duration (minutes)	30	240	15	30	30	60	30	30	240
Clinical Research Facility		X				X			X
Venue of participant's own choice	X			X	X		X	X	
Telephone Call			X						
Information & consent	X								
Demographics	X								
HIV parameters	X					X			X
Diet diary issued	X				X			X	
Diet diary collected		X				X			X
Remind to attend fasting next visit	X				X			X	
24-hour dietary recall			X	X	X		X	X	
FSLMTT		X							X
Fasting glucose, insulin						X			
Lipids, HbA1c		X				X			X
BioBank samples		X							X
Manual anthropometry		X		X	X	X	X	X	X
BIA		X							X
Hand grip strength		X							X
HAT-QoL questionnaire		X							X
IPAQ questionnaire		X							X
Issue with Pedometer		X							
Review pedometer data			X	X	X	X	X	X	X
Smoking history		X							X
Blood pressure		X							X
10 year CVD/T2D risk		X							X
Agreed goal setting		X	X	X	X	X	X	X	
Lifestyle advice given		X	X	X	X	X	X	X	
Adherence to lifestyle			X	X	X	X	X	X	X
Motivational interviewing			X	X	X	X	X	X	
Support discussion			X						
Adverse event monitoring		X	X	X	X	X	X	X	X
Trial exit advice									X

Source: A Duncan

2.6.13 Statistical Analysis, Intervention

Data was collected and entered into a secure Microsoft Excel spreadsheet, then transferred for statistical analysis to SPSS version 22. Distribution of the data was tested. For variables with a normal distribution arithmetic means and standard deviations were calculated. Variables without a normal distribution were considered for log or square root transformation. Medians and interquartile ranges were calculated.

As this was a pilot study, statistical analysis was descriptive with a focus primarily on confidence intervals (CIs) as opposed to statistical significance of rejection of the null hypothesis (Lancaster et al., 2004). Descriptive statistics were used to explore a range of findings including recruitment and completion rates and demographics. Confidence interval estimation at the 95% level were used. Paired t-tests were used to compare the effect of the intervention. Significance levels were set at <0.05 with two-tailed tests.

The relationship between outcomes and adherence to the intervention was explored by classifying participants by number of goals achieved: 6-10 goals - high achievers, 3-5 - moderate and 2 or fewer - poor achievers (Oakley et al., 2006). Future risk of developing CVD and T2D was estimated using the QRisk2 and QDiabetes equations respectively. It was anticipated that there would be insufficient power to assess differences between subgroups of participants using regression analysis.

2.7 Qualitative Study

In these sections I briefly introduce concepts underpinning qualitative research in healthcare, my philosophical position and how this might bias conduct of this study, and background to selection of methodology. Sampling, data collection and data analysis procedures are outlined.

2.7.1 Introduction to Qualitative Research

Historically, health researchers utilised objective natural science methodologies. Over time phenomena were measured at increasingly minute levels in the pursuit of perceived accuracy. This philosophy, reductionist and positivist in nature, facilitated advances in quantitative research methodologies somewhat at the expense of qualitative approaches (Rachael Ormston, 2014). More recently, healthcare researchers in addition to asking "how many" have been asking "why" and "how", and indeed the MRC now advocates for inclusion of qualitative research methodology at all stages of development of complex interventions (Craig et al., 2008). Qualitative methods are increasingly used alongside quantitative methods in RCTs (Lewin et al., 2009). Qualitative methods can help develop an understanding of how to implement research findings into routine clinical practice (Kennedy et al., 2014) and have been used to identify modifiable factors for improving health care (Wright et al., 2004). However, as the training of health care professionals remains rooted in laboratory and basic sciences governed by natural laws, it is not surprising that investigators conducting a broad review of health-related studies concluded that taken as a whole research methodology remains overwhelmingly quantitative (Crawford et al., 2003).

The underlying theories methods or practice of qualitative research can be difficult to clearly define due to the heterogeneity of its nature (NK and YS, 2011). However, qualitative research can be very broadly defined as the collection, analysis and interpretation of non-numerical data, referring to research methods focussing on the importance of context for the data being examined and a deeper understanding of any phenomenon. Qualitative research generates new knowledge, understanding and perspectives, and is being used increasingly in health care investigations, including both HIV (Power, 1998) and diabetes related research (Seale et al., 2013). Diet and physical activity can have a significant impact on the health of people living in the UK and qualitative research methods are well-suited to investigating behaviours influenced by social, cultural and material circumstances (NICE, 2014a). A broad range of non-

standardised and adaptable investigative methods can be utilised. However, in health care most qualitative research investigators have used interviews and focus groups (Sofaer, 2002). Data generated is rich and complex. Analysis of this data retains its complexity whilst at the same time respecting the uniqueness of the individual participant. Qualitative researchers are open to emerging theories. They acknowledge their role and personal perspectives within the research process, maintaining a reflexive approach (Rachael Ormston, 2014).

A wide range of techniques and approaches is used in qualitative healthcare studies. Ethnography, where the researchers immerse themselves within and directly observe the behaviour of the cohort, was used to investigate decision making by GPs (Gabbay and le May, 2004). This was voted as one of the most influential British Medical Journal papers published in the last 20 years (Payne, 2015). The meaning people attach to a phenomenon or how they make sense of their social world is explored using phenomenology, and this approach has been used to study body image in gay men (Kelly et al., 2009). Grounded theory employs systematic collection and analysis of data from participants in order to generate emergent theory regarding social processes or actions (Glaser, 1967). During the initial outbreak of severe acute respiratory syndrome (SARS) in 2003, researchers used grounded theory to investigate the impact of the outbreak on physicians' behaviour and professionalism (Straus et al., 2004). Thematic analysis of data involves systematic examination to identify topics, gradually and progressively integrated into higher order themes. Analysis aims to answer research question(s). This technique is widely used in healthcare research and can be applied to data generated by several of the approaches listed in this section (Chapman et al., 2015).

2.7.2 Positionality, Methodological Position and Bias

The theoretical perspectives discussed in the previous section underpin my choice of methodology for data collection, analysis, and interpretation. The majority of qualitative research studies employ an interpretivist approach in which the focus is on how participants make sense of their experiences through studying social or behavioural phenomena. However, there is a perceived risk that qualitative research can be subjective, with the researcher's background affecting aims and objectives, planning, design, analysis and interpretation (Guillemin and Gillam, 2004). Acknowledging bias can help the researcher and reader appreciate any contributions this might have made to the work. In order to understand a phenomenon neutrally and fully, some qualitative researchers have claimed that they have

been able to compartmentalise biases or personal beliefs in a process referred to as bracketing (Sorsa et al., 2015). Others have highlighted the value of intimacy and familiarity between researcher and participant (Charmaz, 2004). The degree of success of bracketing to set aside prior understanding and act without judgement cannot be measured. Irrespective of the avoidance or success of bracketing it is important to consider researcher reflexivity and how personal experience and knowledge may have influenced the research study.

Given my background in nutritional science, clinical dietetics and quantitative research I acknowledge the duality of my positivist and interpretivist approaches to this study. My extensive experience of one-to-one clinical interviews lent itself to choosing in-depth interviews to collect data from participants. I am aware that clinical interviewing is distinct from in-depth interviews for research. Both aim to elicit information and experiences. However, in the clinical situation the interviewer clearly directs the process in order to identify information important to their work, whereas in research practice any direction by the interviewer aims to allow expression of feelings or description of phenomena important to the interviewee (Hunt et al., 2011). I took note of the potential for power dynamics, different use of language and cues, and of mixed messages, for example by wearing a clinical identification badge during the interview. I positioned the interviewee as the expert and explained my role was now different before commencing each interview.

My positivist approach from experience in science and quantitative research led to the development of semi-structured interviewing and the use of Framework for analysis of data. I felt it would be more productive to use a topic guide as I was concerned that use of open interviews might result in the generation of a narrow focus of data. The use of the structured Framework approach was a pragmatic choice given the limited time available for analysis.

In terms of potential for bias, I developed this qualitative study with prior clinical experience of HIV patients' enablers and barriers to lifestyle change. Although this prior knowledge was useful to inform design of the interview topic guide, I aimed to remain open to the possibility that interviewees would describe different enablers or barriers, and attribute them varying degrees of importance. There was the potential to have had a high degree of personal involvement in the participant's routine health care. Participants recruited from St. Thomas' hospital may have received clinical care from me prior to taking part in the research study, as well as taking part in the 6-month intervention.

2.7.3 Rationale for Design of the Qualitative Study

This qualitative study was designed to answer the following research questions:

- What was the acceptability of the intervention?
- What enablers, barriers and other factors influenced lifestyle change?
- In this cohort, what influences participation in medical research?

To answer the first and third of these questions, either interviews or focus groups could both yield rich data.

Focus groups are semi-structured discussions with groups of typically between four and twelve participants. In qualitative health care research they are used to explore issues in a similar way to interviews (Rachael Ormston, 2014). Investigators moderating focus groups follow a typical structure of introducing the topic in a broad sense in order to develop group dynamics before focussing on key questions specific to the research question(s). Through the group structure investigators are able to explore individual and shared perspectives (Sofaer, 2002). Disadvantages of focus groups include logistics of organisation, potential for breach of confidentiality or the presence of a dominant person who may disrupt the group dynamic. Where subject matter is particularly sensitive individual participants may be unwilling to discuss experiences in a group setting, although conversely shared experience from focus groups can be positively empowering (Rachael Ormston, 2014).

The effectiveness of complex interventions varies between individuals and I anticipated that there would be variations in the individual effectiveness of this intervention dependent on, for example, sociocultural settings (Pope and Mays, 1995). Given the potential for sensitive issues to be raised regarding enablers and barriers and my extensive experience of clinical interviews with patients, I chose one-to-one in-depth interview methodology.

Thematic analysis was used to seek support for predefined and also emerging hypotheses. In-depth interviews aim to explore the experiences and social behaviour of participants and the meanings they attribute to these experiences. Investigators encourage participants to discuss topics relevant to the research question(s) using open questioning, usually in one-to-one interviews although other structures have been used including dyads and family units. Interviewers in semi-structured approaches use a topic guide and will probe topics relevant to the research question. In health care qualitative research, in-depth interviews often explore

the experiences and personal meaning of illness or disease. Personal issues can be openly and sensitively explored (Sofaer, 2002).

Open or unstructured interviews set a single question with the participant subsequently speaking freely without interruption. Structured interviews employ a predefined series of questions (Sofaer, 2002). Semi-structured interviews were used for this study in order to provide structure with flexibility, where predefined themes for questioning were used as the starting point with the interviewer probing further or clarifying answers with the participant.

The choice of semi-structured in-depth interviews to generate data had practical advantages over other methods. The use of ethnography would be logistically impractical and a case study approach would not foster iterative development of thematic analysis. Grounded theory could not apply to this study as I had explored predefined themes, and employed patient public involvement. Finally, in terms of logistics, one-to-one interviews could be arranged to take place shortly after a decision not to participate in the intervention, or after dropping out or completing the intervention.

Framework was selected to analyse qualitative data. This matrix-based summary of data organised by theme and sub-theme in columns and participants in rows allows the researcher to conduct cross-case and cross-theme analysis, and aids construction of typologies (Smith and Firth, 2011). I selected this approach for practical reasons. Time constraints within the project demanded a systematic approach to thematic analysis. Framework confers the ability to rapidly apply themes from each interview to the construct, allowing immediate analysis. Following receipt of each interview transcript, initial familiarisation involved rereading and re-listening. This was followed by identification of possible themes and sub-themes. These were coded using short statements to capture the meaning of the phrase. Data was imported into NVivo11™ software (QSR International). Initial thematic analysis resulted in completion of the framework matrix for that participant.

Thematic analysis has been criticised for the potential to isolate fragments of data from the whole, leading to a possible misinterpretation of the data (Smith and Firth, 2011). To reduce this possibility I introduced a final re-reading of interview transcripts prior to moving towards constructing typologies.

2.7.4 Sampling Structure for the Qualitative Study

Whereas quantitative research aims to identify typical or mean data, qualitative research aims to both explore and present the breadth of data from an investigation. This may include extreme, atypical or outlying views and also an absence of views or experiences. In qualitative research rather than sampling to statistically represent the population a generalisable sample is sought where participants express the diversity of views and experiences.

Participants were invited to interview if:

- They were eligible but declined to take part in the intervention
- They wished to take part in the intervention but on screening were found to be ineligible
- They dropped out, withdrew, or were withdrawn during the intervention
- They completed the intervention

Participants were purposively selected to include representatives of each of these 4 categories. Additionally, to include maximum diversity participants were purposively sampled from the following groups:

- Gay men who exercise
- Gay men with a higher BMI
- Black African-origin men
- Black African-origin women

For budgetary and logistical reasons the sample size was set at a maximum of 40 participants. The actual number invited to interview was determined at the point at which I was satisfied that a good understanding of the acceptability of the intervention and also of enablers and barriers to change had been achieved. Within the purposive sampling methodology recruitment from a particular group ceased when no new data was emerging from that group. In a review of analysis of qualitative data, investigators found that on average 10 interviews were required to reach data saturation (Francis et al., 2010) and given four groups sampled for diversity this married well with the maximum sample size of 40. The use of Framework to analyse data as interviews progressed facilitated ongoing assessment of emerging data.

2.7.5 The Interview

Informed consent to take part in the interview was taken or revisited according to the participant's journey through the three studies presented in this thesis. All participants were offered a choice of interviewer: myself or a health adviser (trained counsellor) from the HIV clinic. I am a White male. Given the potential for a number of African-origin participants to be invited to interview I engaged a Black-African female health adviser to be an alternative interviewer. Interviews were conducted at a place and time to suit the participant. Venues offered were:

- The participant's own home or workplace
- A meeting room in a non-clinical area of St. Thomas' Hospital
- An interview room in the Clinical Research Facility at St. Thomas' Hospital
- A consultation room at the premises of the charity Terence Higgins Trust near King's Cross

Prior to conducting the interviews I completed a qualitative research training programme at the Institute of Psychiatry and at NATCEN in London, both of which included components of interviewing structure and techniques.

The review I conducted presented in Section 1.7 identified little published research regarding enablers and barriers to diet and exercise change in PLWH. Research papers describe attitudes towards body image in PLWH, particularly in relation to those experiencing lipodystrophy. Together with findings from my review of non-HIV specific literature regarding enablers and barriers to diet and exercise change presented in Table 1.11 and suggestions from clinical practice that there may be potential for patients to experience HIV-specific barriers to lifestyle change, questions regarding these were developed and included in topic guides.

Three topic guides were developed (Appendix 7). The topic guides were for: (1) those who declined to take part in the 6-month intervention, (2) those who dropped out of the intervention and (3) those who completed the intervention. Topic Guide 3 evolved over the course of the study reflecting the iterative nature of the work, and the final version used is presented in Appendix 7. As the interviews and Framework analysis progressed iterative themes were incorporated into the design of topic guides to minimise confirmatory bias, ensuring that the direction of data collection was informed by the participants.

Open questions, active listening and asking relevant follow-up questions were used to probe, amplify or expand themes. Mapping questions were used to contextualise experiences. Styles of questioning developed following participant response as interviews progressed.

Interviews were digitally recorded. Recordings were transcribed verbatim, with notes of pauses, mannerisms and audible behaviour included. Prior to analysis I replaced any identifiable information with contextual description, for example removing the actual name of a partner mentioned and inserting "partner's name". I transcribed the first six interviews, with subsequent recordings transcribed commercially. Participants were offered a copy of the transcript of the interview.

2.7.6 Analysis

Data analysis was an iterative process where data collection and analysis occurred concurrently using the Framework approach. Codes were combined and contrasted, developing themes and categories of themes that grouped similar codes together. This enabled a synthesis generating a network of associations. Themes emerging from the analysis were checked against new data as transcripts were added using NVIVO, and influenced ongoing data collection. Analysis of enablers and barriers to behaviour change was aided by using the COM-B and Theoretical Domain Framework models (Cane et al., 2012, Michie et al., 2011b).

In the later stages of analysis themes emerging from the coded data were used to construct typologies. Collaborator Dr Carol Rivas and supervisor Dr Louise Goff jointly checked and discussed thematic analysis to improve rigour of findings.

Continuous analysis of data allowed assessment of thematic saturation, where no new significant data was emerging from the analysis grouped according to purposive sampling. Recruitment to interview ceased at this point.

3 RESULTS

> *'Interviewer: "You said that you were happy that you reduced your waist, is that right?"*
>
> *Interviewee: "Right, but I wasn't happy with the effect on my face. I'd rather have diabetes and a full face. So I'd rather be a diabetic injecting myself every day, than look like I look now"'*

3.1 Participant Recruitment and Welfare

3.1.1 Recruitment

Three hundred and thirty-nine participants took part across the portfolio of research: 338 in the phenotype of type 2 diabetes in HIV study, 33 in the 6-month intervention, and 23 were interviewed. All 33 intervention participants and 22 of the 23 interview participants consented to contribute data to the phenotype study, and these 55 are included in the total of 338.

Figures 9 and 10 describe the Consort Flow Diagrams for screening, phenotype, intervention and qualitative studies. Patients were largely identified by me, with 4% referred by others and 1% self-referring in response to advertising. Thirteen percent did not respond to an invitation to be screened to take part and 33% declined to be screened. Following good practice guidelines (Health Research Authority, 2016), patients were not asked directly why they declined, but of the 104 who mentioned reasons the commonest were: research fatigue (38%), problematic logistics (34%) and a lack of interest in research (14%). Of the 1572 patients screened 2% had never had blood glucose measured and 6% had raised random blood glucose measured in routine clinical blood screening but were unwilling or unable to attend fasting. A

total of 1447 patients had fasting blood glucose results, with 69% having normal blood glucose, 24% prediabetes defined by IFG, and 14% had type 2 diabetes. Of the 1447 patients stratified by glycaemia, 821 (57%) declined to take part, 167 (12%) did not meet inclusion criteria, 339 (25%) took part in one or more of the three research studies and 120 (8%) did meet inclusion criteria but were surplus to sample. Reasons for exclusion from the phenotype study were: unable to provide informed consent (31%), unable to communicate in English (31%), unable to attend for data collection (19%), too unwell to take part (13%), currently serving a custodial sentence (4%) and type 1 diabetes (2%). Reasons for exclusion from the intervention were: unable to commit to a 6-month programme (33%), infectious hepatitis (28%), use of medications associated with dysglycaemia (17%), naïve to ARVs (17%) and pregnancy (5%). Stratified sampling targets for the phenotype study (Table 2.2 on page 68) were achieved.

3.1.2 Participant Welfare

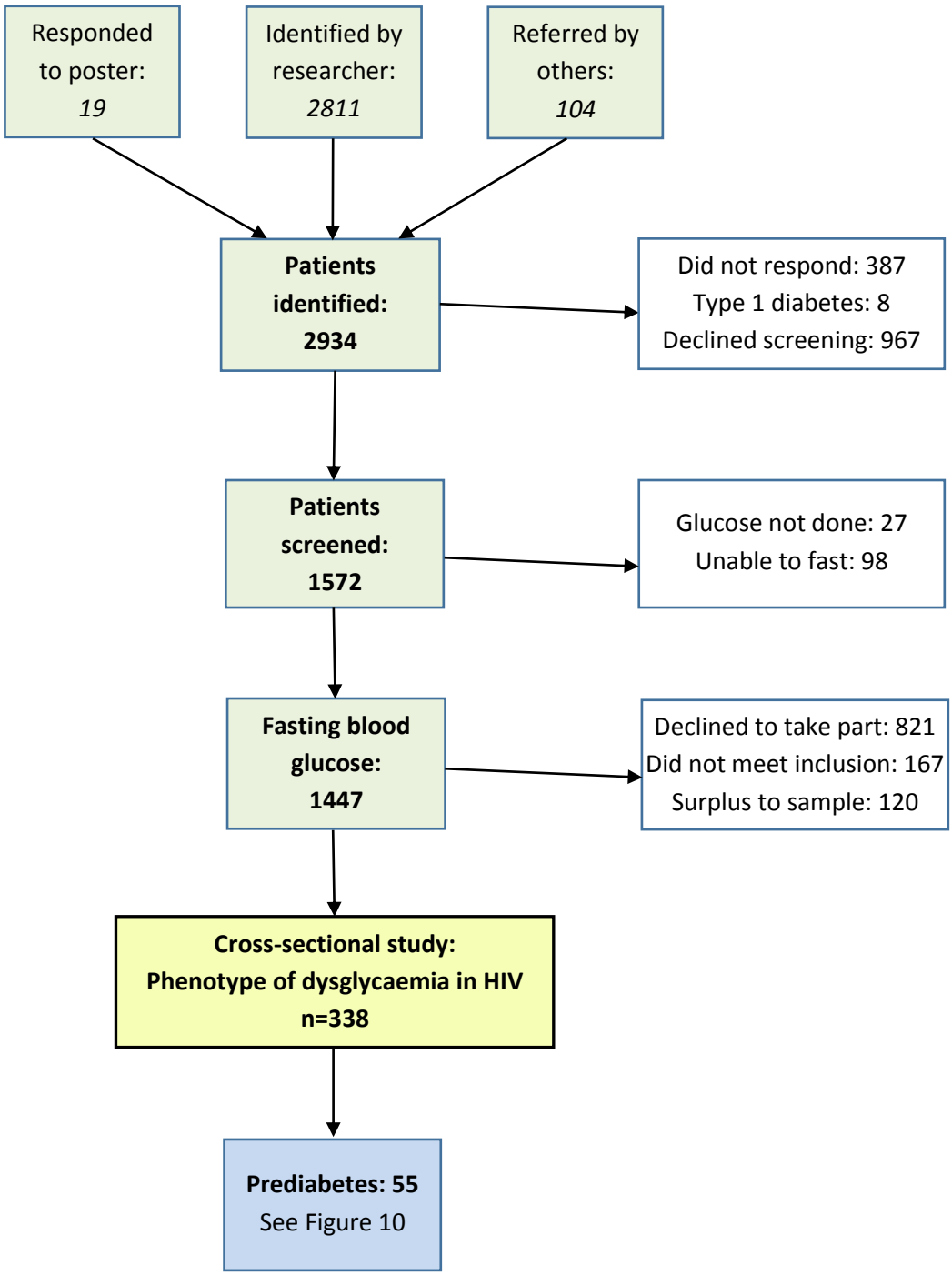
During the 6-month intervention study, four participants experienced adverse events (AEs) thought to be unrelated. Participant 1 experienced a severely sprained ankle caused by losing balance when getting out of bed during the night. This occurred during month 2 of the intervention and limited physical activity for 2 weeks but was insufficient to consider withdrawal from the study. This participant consented to take part in an in-depth interview where their deep unease with facial weight loss was discussed for the first time, and subsequent referral for counselling was made.

Participant 2 experienced an episode of fainting mid-way through the FSLMTT at baseline. This required medical attention at Accident and Emergency secondary to extremely low blood pressure. It was subsequently discovered that the participant's GP had prescribed an incorrect dose of antihypertensives resulting in hypotension. The participant requested to re-start the intervention once this was remedied. Participants 3 and 4 were diagnosed with T2D at baseline, withdrawn from the intervention and given advice as per protocol. GPs and HIV physicians were informed. Both participants subsequently consented for interview.

A participant withdrew from the intervention at month 2 on becoming acutely unwell at home. On admission to hospital they were diagnosed with bacterial septicaemia. This participant later consented to take part in an in-depth interview.

3.1.3 Recruitment: Consort Flow Diagrams

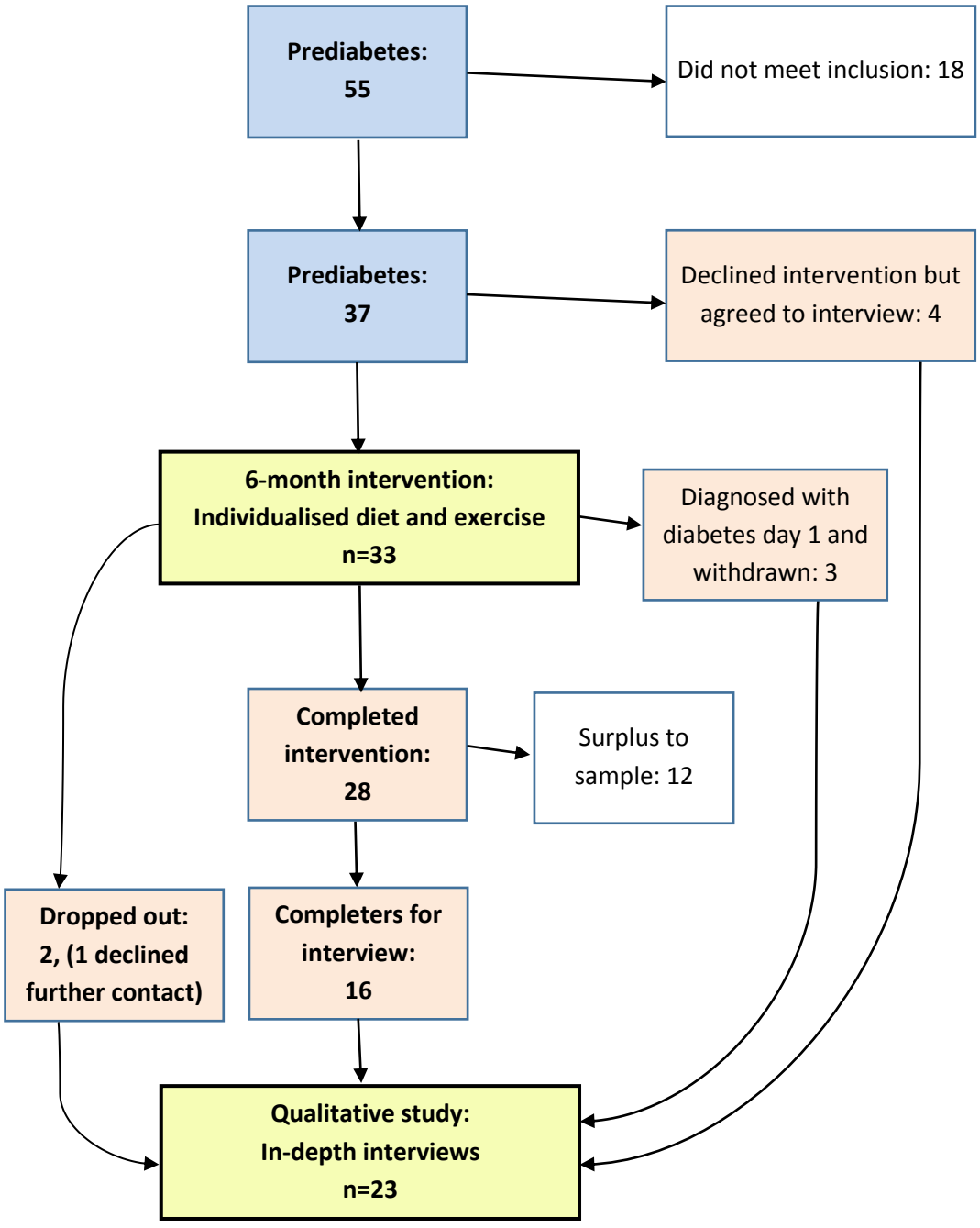
Figure 9: Consort Flow Diagram, Part 1 – Screening and Phenotype Study



Notes:

- Reasons for exclusion of 167 participants: unable to provide informed consent (52), insufficient English language skills (52), unable to attend (32), unwell (22), other (9)
- 120 participants were surplus to the stratified random sample. Participants were sampled by age, gender and ethnicity

Figure 10: Consort Flow Diagram, Part 2 - Intervention and Interviews



Notes:

- Reasons for exclusion of 18 participants: unable to commit to a 6-month programme (6), infectious hepatitis (5), use of medicines associated with dysglycaemia (3), naïve to ARVs (3), pregnancy (1)
- 13 participants were surplus to purposive sample. Participants were sampled by ethnicity, sexuality and exercise behaviour

3.2 Phenotype of Dysglycaemia in HIV

3.2.1 Principal Results Summary

It was hypothesised that in HIV patients, BMI and a range of other factors are independently associated with impaired fasting glucose and type 2 diabetes when compared to patients with normal fasting glucose. The aim of this study was to phenotype dysglycaemia in this cohort, and describe how this has changed over time.

Principal Results:

- Dysglycaemia is highly prevalent in this ethnically diverse HIV cohort
- In 2015 the mean duration of HIV infection was 11.6 years, and 92.0% were treated with ARVs, 58.0% were overweight or obese, 62.4% had central obesity, and 37.9% had hypertension, with Black African women disproportionately affected by obesity
- The prevalence of T2D in 2005 was 6.8%, and in 2015 was 15.1%
- Dysglycaemia was significantly associated with age, BMI, waist, hypertension, HDL, triglycerides, CVD, statin use, 10-year CVD risk, HIV duration, exposure to ARVs associated with T2D, weight gain following initiation of ARVs, lipodystrophy, hepatic steatosis, use of corticosteroids, physical inactivity, socioeconomic deprivation and unemployment
- Regression models suggested that modifiable factors contribute a greater risk of dysglycaemia than fixed factors, most of which were HIV-related
- Hepatic steatosis and hypertension contributed the greatest risk with odds ratios of 7.28 and 2.58 respectively

3.2.2 Analysis of Data Collected in 2005-2006

Retrospective analysis of data from the CREATE study revealed missing blood glucose data for the majority of participants. Out of the 1021 participants 337 had confirmed fasting glucose data. The sample was tested for statistical representation of the cohort when analysed by 16 demographic, medical and HIV-related factors. The sample of 337 participants was representative for all measures (Table 3.1).

Table 3.1: Sensitivity Analysis for 2005 Sample and Total Cohort

		†CREATE n=337	††CREATE n=1021	*p*
TOTAL	n	337	1021	
GENDER	Male	260 (77.2%)	764 (74.8%)	0.265[a]
AGE	Mean years	41.7	40.4	0.134[b]
ETHNICITY	White	184 (54.6%)	512 (50.1%)	0.407[a]
BMI	Mean kg/m^2	25.8	25.5	0.835[b]
WAIST	Mean cm	91.3	90.1	0.132[b]
HYPERTENSION	n	66 (19.6%)	192 (18.8%)	0.891[a]
LIPIDS (mean)	Total Cholesterol	4.8	4.7	0.794[b]
mmol/l	Triglycerides	1.8	1.7	0.237[b]
CURRENT SMOKER	n	120 (35.6%)	378 (37.0%)	0.326[a]
CVD	n	9 (2.7%)	32 (3.1%)	0.563[a]
STATIN USE	n	54 (16.0%)	129 (12.6%)	0.268[a]
HIV DURATION	Mean years	6.3	6.5	0.249[b]
ARV NAIVE	n	66 (19.6%)	223 (21.8%)	0.426[a]
LIPODYSTROPHY	n	92 (27.3%)	216 (21.2%)	0.336[a]
HEPATITIS B	n	15 (4.4%)	50 (4.9%)	0.981[a]
HEPATITIS C	n	12 (3.6%)	34 (3.3%)	0.831[a]

NOTES
† Glycaemia measured
††Total sample including glycaemia not measured
[a] Significance of difference by Chi-squared
[b] Significance of difference by ANOVA

Participants were stratified according to glycaemia by either a recorded diagnosis of T2D or a confirmed fasting glucose: normal (≤5.9 mmol/l); prediabetes (6.0-6.9 mmol/l); and T2D (≥7.0 mmol/l). Characteristics of the 2005 sample are presented in Table 3.2.

In 2005 18.1% had prediabetes and 6.8% T2D, higher than that reported in the data published from the CREATE study due to a redefined classification of T2D to include fasting glucose of 7.0 mmol/l or higher. The cohort had a median age of 41 years, was predominately male (77.2%), ethnically diverse (45.4% non-White) and largely treated with ARVs (80.4% for a mean 6.3 years). One-quarter (23.4%) had been exposed to ARVs associated with insulin resistance and 27.3% had current or previous lipodystrophy. One-third were smokers but mean 10-year CVD risk measured by the Framingham tool was low (4.4%) which may reflect the modest lipids levels observed (mean total cholesterol 4.8 ±1.0 mmol/l) and the relatively young median age. Hepatitis coinfection rates were low.

Table 3.2: Characteristics of the 2005 Sample

		Normal	Prediabetes	T2D	Total
TOTAL	n	253	61	23	337
	% of total	75.1%	18.1%	6.8%	100.0%
GENDER	Male	76.7%	78.7%	78.3%	77.2%
AGE (Years)	Median (IQR)	40 (35-46)	43 (38-48)	46 (44-54)	41 (35-47)
ETHNICITY	White	56.1%	49.2%	52.2%	54.6%
	Black African	27.3%	31.1%	30.4%	28.2%
	Black Caribbean	4.7%	9.8%	8.7%	5.9%
	Other	11.9%	9.8%	8.7%	11.3%
BMI	Median (kg/m^2)	25.0	23.7	24.0	24.9
	IQR	22.6-27.9	22.3-28.1	21.9-28.3	22.4-28.0
	Underweight (<18.5 kg/m^2)	3.2%	1.6%	0%	2.7%
	Normal (18.5-24.9 kg/m^2)	46.6%	57.4%	56.5%	49.3%
	Overweight (25.0-29.9 kg/m^2)	34.4%	27.9%	21.7%	32.2%
	Obese (≥30.0 kg/m^2)	15.8%	13.1%	21.7%	15.7%
WAIST (IDF DEFINITION)	Obese	44.5%	53.6%	68.4%	47.7%
	Median (cm)	89	94	96	91
	IQR	81-97	88-101	91-110	83-98
HYPERTENSION	n	15.4%	27.9%	43.5%	19.6%
LIPIDS (mmol/l)	Total Cholesterol	4.8	5.1	4.7	4.8
	SD	1.0	1.2	1.0	1.0
	HDL: TG Ratio	1.50	1.91	1.65	1.59
	SD	1.83	1.52	1.07	1.74
METABOLIC SYNDROME		13.8%	46.4%	52.6%	22.5%
SMOKING	**No**	63.6%	63.9%	65.2%	63.8%
	Yes	36.4%	36.1%	34.8%	35.6%
CVD (including CVA)		2.0%	3.3%	8.7%	2.7%
STATIN USE		14.1%	28.0%	26.7%	16.0%
% 10-YEAR CVD RISK	**Mean**	4.2	5.0	5.2	4.4
(Framingham)	SD	5.3	5.7	4.9	5.4
HIV Duration (years)	Mean	6.0	7.1	7.8	6.3
	SD	0.9	0.9	0.9	0.9
NAÏVE TO ARVs		22.5%	11.5%	8.7%	19.6%
ARVs ASSOCIATED WITH T2D		23.7%	18.0%	34.8%	23.4%
LIPODYSTROPHY		22.1%	37.7%	56.5%	27.3%
HEPATITIS B		4.3%	4.9%	4.3%	4.5%
HEPATITIS C		2.8%	3.3%	13.0%	3.6%

Note: Variables as defined in section 2.5.4

3.2.3 Cohort Characteristics in 2015

Characteristics of the 338 participants in the 2015 cohort are presented in Table 3.3. In terms of dysglycaemia, 17.2% had prediabetes and 15.1% T2D. The cohort had a median age of 49 years (IQR 42-57) and was predominately male (74.0%). This cohort was ethnically diverse with the majority (50.3%) non-White. The 338 participants were born in 61 countries as illustrated in Figure 11, with the five most common being the UK (n=127), Uganda (n=26), Nigeria (n=19), Zimbabwe (n=10) and Jamaica (n=9).

The cohort was highly treated with ARVs (92.0%), with a mean duration of treatment of 11.6 ±0.9 years. Exposure to ARVs is presented in Table 3.4. Just under half (44.1%) had been exposed to ARVs associated with insulin resistance and one-fifth (21.6%) had current or historic lipodystrophy. Taken as a whole the cohort was overweight with a mean BMI of 27.4 kg/m^2 (IQR 23.3-29.9), with the majority (62.4%) presenting with central obesity. The high rate of hypertension (37.9%) combined with central obesity resulted in almost one-third of the cohort (31.8%) presenting with metabolic syndrome. Of the two-fifths with a smoking history, half had successfully quit smoking (19.8% of the cohort) and half were current smokers (21.0% of the cohort). The mean 10-year CVD risk measured by the Framingham tool was 12.1% with 27.2% of the cohort treated with statins. Hepatic steatosis had been diagnosed in 21.0% and renal impairment in 12.7% of the cohort. Almost half (48.1%) had a first or second degree relative with T2D. Vitamin D had been measured in 200 participants with a mean of 57 ±27 nmol/l.

'Table 3.3: Characteristics of the 2015 Cohort

		Normal	Prediabetes	T2D	Total
TOTAL	n	229	58	51	338
	% of total	67.8%	17.2%	15.1%	100.0%
GENDER	Male	167	45	38	250
		72.9%	77.6%	74.5%	74.0%
AGE (Years)	Median	47	53	54	49
	(IQR)	(39-55)	(47-60)	(48-62)	(42-57)
ETHNICITY	White	117	31	20	168
		51.1%	53.4%	39.2%	49.7%
	Black African	70	17	20	107
		30.6%	29.3%	39.2%	31.7%
	Black Caribbean	15	2	7	26
		6.6%	6.9%	13.7%	7.7%
	Other	27	6	4	37
		11.8%	10.3%	7.8%	10.9%
BMI	Median (kg/m^2)	25.3	27.6	29.0	27.4
	IQR	22.7-29.3	24.7-32.0	24.8-31.2	23.3-29.9
	Underweight (<18.5 kg/m^2)	5	2	1	8
		2.2%	3.4%	2.0%	2.4%
	Normal (18.5-24.9 kg/m^2)	107	15	12	134
		46.7%	25.9%	23.4%	39.6%
	Overweight (25.0-29.9 kg/m^2)	69	23	24	116
		30.1%	39.7%	47.1%	34.3%
	Obese (≥30.0 kg/m^2)	48	18	14	80
		21.0%	31.0%	27.5%	23.7%
WAIST (IDF Definition)	Obese	123	43	45	211
		53.7%	74.1%	88.2%	62.4%
	Median (cm)	92	101	103	95
	IQR	84-101	92-101	93-112	86-104
HYPERTENSION	n	57	31	40	128
		24.9%	53.4%	78.4%	37.9%
LIPIDS (mmol/l)	Total Cholesterol	5.0	4.9	4.9	5.0
	SD	1.1	1.0	1.2	1.1
	LDL[a]	2.89	2.81	2.58	2.83
	SD	0.90	1.04	0.84	0.92
	HDL: TG Ratio	1.17	1.71	2.04	1.39
	SD	0.96	1.33	1.63	1.19
METABOLIC SYNDROME		26	42	39	107
		11.4%	72.4%	76.5%	31.8%
SMOKING	No	135	36	29	200
		59.0%	62.1%	56.9%	59.2%
	Yes	56	8	7	71
		24.5%	13.8%	13.7%	21.0%
	Ex-smoker	38	14	15	67
		16.6%	24.1%	29.4%	19.8%
CVD (excluding stroke)		9	5	5	19
		3.9%	8.6%	9.8%	5.6%

		Normal	Prediabetes	T2D	Total
STROKE[a]		5	3	4	12
		2.2%	5.2%	7.8%	3.6%
STATIN USE		34	22	36	92
		14.8%	37.9%	70.6%	27.2%
% 10-YEAR CVD RISK	Mean	9.0	12.6	25.5	12.1
(Framingham)	SD	9.2	10.1	16.9	12.3
HIV Duration (years)	Mean	10.4	13.9	14.8	11.6
	SD	0.9	0.9	0.9	0.9
ARV Naïve		22	2	3	27
		9.6%	3.4%	5.9%	8.0%
ARVs ASSOCIATED WITH T2D		88	31	30	149
		38.4%	53.4%	58.8%	44.1%
% WT. GAIN FOLLOWING	Mean	3.1%	7.0%	10.1%	4.9%
INITIATION OF ARVs[a]	SD	7.9	11.0	15.6	10.4
LIPODYSTROPHY		40	14	19	73
		17.5%	24.1%	37.3%	21.6%
HEPATITIS B		23	5	3	31
		10.0%	8.6%	5.9%	9.2%
HEPATITIS C		11	4	1	16
		4.8%	6.9%	2.0%	4.7%
CD4 NADIR	Mean	225	186	191	213
	(±SD)	(189)	(125)	(188)	(180)
VITAMIN D[a,b] (nmol/l)	Mean	53	46	47	51
	(±SD)	(27)	(28)	(26)	(27)
HEPATIC STEATOSIS[a]		19	27	25	71
		8.3%	46.6%	49.0%	21.0%
RENAL IMPAIRMENT[a]		24	7	12	43
		10.5%	12.1%	23.5%	12.7%
CORTICOSTEROIDS[a]		51	21	17	89
		22.3%	36.2%	33.3%	26.3%
RELATIVE T2D[a,c]		103	31	29	163
		44.7%	53.4%	56.9%	48.1%
PHYSICAL ACTIVITY[a]	Mean (±SD)	3.3	1.7	1.4	2.7
(Hours/week)		(4.3)	(3.8)	(2.6)	(4.1)
FRUIT & VEG[a]	Mean (±SD)	3.5	3.2	3.3	3.4
(Portions/day)		(1.5)	(1.6)	(1.5)	(1.5)
FURTHER EDUCATION[a]		183	44	34	261
		79.9%	75.9%	66.7%	77.2%
SOCIOECONOMIC NSEC	Mean	4.6	4.9	6.4	4.9
SCALES[a]	(±SD)	(2.8)	(2.8)	(2.4)	(2.8)
MacArthur UK	Mean	4.9	4.7	4.2	4.8
	(±SD)	(1.8)	(1.7)	(1.7)	(1.8)
MacArthur Community	Mean	6.5	6.7	6.5	6.5
	(±SD)	(1.6)	(1.8)	(1.7)	(1.7)
EMPLOYMENT[a] Working or Student		153	37	18	208
		66.8%	63.8%	35.3%	61.5%
Unemployed		60	15	25	100
		26.2%	25.9%	49.0%	29.6%

	Normal	Prediabetes	T2D	Total
Retired	16	6	8	30
	7.0%	10.3%	15.7%	8.9%
FINANCIAL STRUGGLE[a]	41	8	12	61
Current	17.9%	13.8%	23.5%	18.0%

Notes:
Variables are as defined in section 2.5.4
The variables duration of HIV infection and duration of treatment with ARVs were highly correlated (Pearson's correlation = 0.847, p<0.001) with the latter not used for further analysis.
a – Measured in 2015 but not in 2005
b – n=200 (not routinely measured clinically)
c – n=337 (unknown due to adoption)
Abbreviations: BMI – Body Mass Index; IDF – International Diabetes Federation; IQR – Interquartile Range; NSEC – National Socioeconomic Scale; SD – Standard Deviation

Figure 11: Cohort Diversity: Participant's Countries of Birth

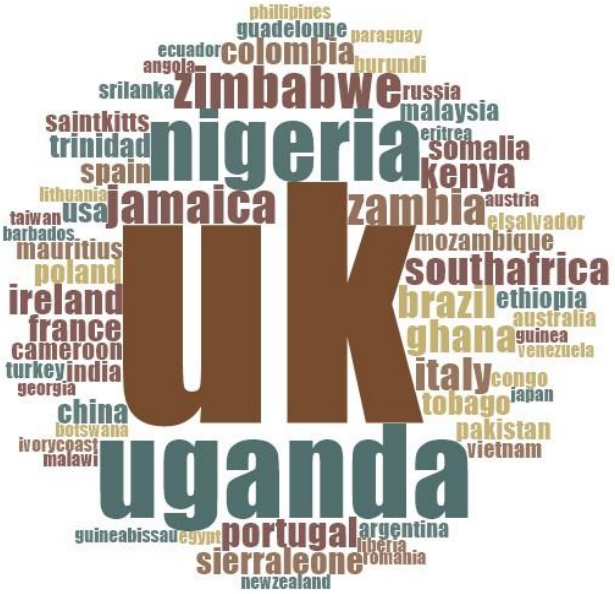
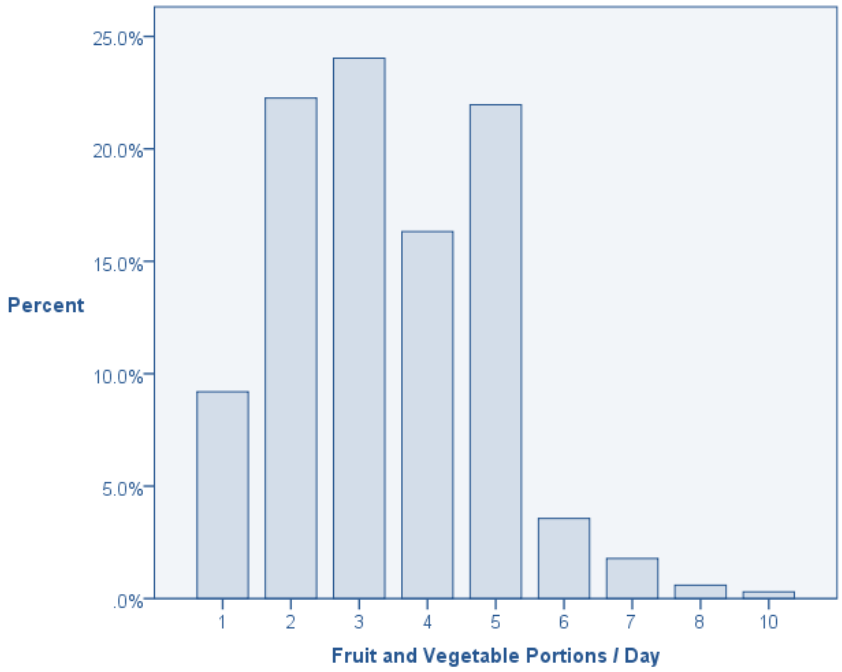


Table 3.4: Antiretroviral Exposure, 2015 Cohort

Generic Name	Brand Name	Participant Exposure (n)	Reported Association With Diabetes Risk	Drug Class
Tenofovir		251		NRTI
Emtricitabine	FTC	205		NRTI
Lamivudine	3TC	181		NRTI
Ritonavir		166	✓	PI
Efavirenz		154		NNRTI
Zidovudine	AZT	124	✓	NRTI
Abacavir		121		NRTI
Atazanavir		92		PI
Darunavir		90		PI
Nevirapine		86		NNRTI
Didanosine	ddI	63	✓	NRTI
Lopinavir	Kaletra	63		PI
Stavudine	d4T	60	✓	NRTI
Saquinavir		43		PI
Raltegravir		38		Integrase Inhibitor
Nelfinavir		29		PI
Fosamprenavir		24		PI
Rilpivirine		22		NNRTI
Zalcitabine	ddC	19	✓	NRTI
Maraviroc		15		CCR5 antagonist
Indinavir		13	✓	PI
Etravirine		10		NNRTI
Amprenavir		4		PI
Enfuvirtide	T-20	3		Fusion Inhibitor
Cobicistat		2		CYP3A Inhibitor
Delavirdine		1		NNRTI
Dolutegravir		1		Integrase Inhibitor
Elvitegravir		1		Integrase Inhibitor
Tipranavir		1		PI

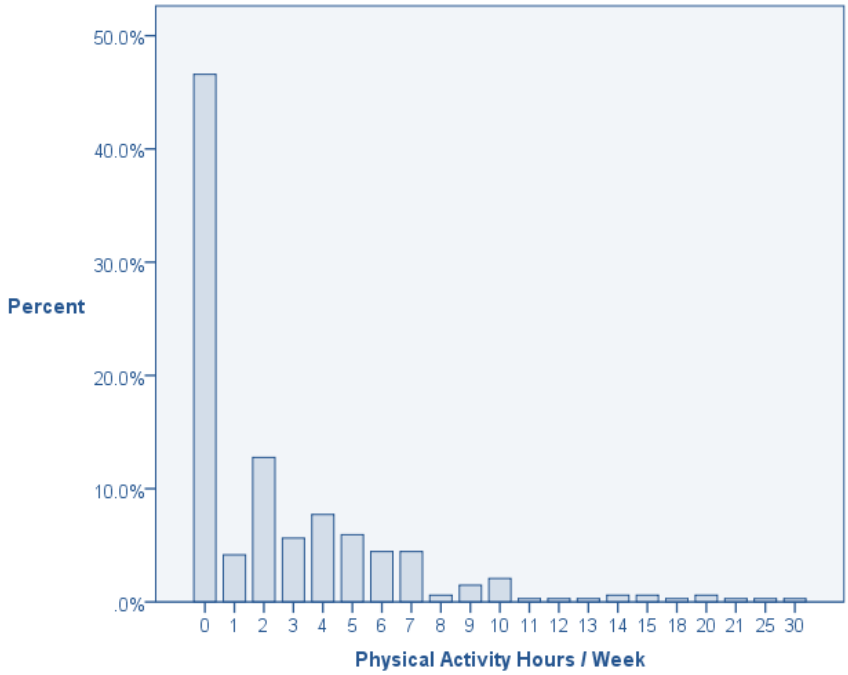
Given the piloting of a diet and exercise intervention, the relationship between these factors and dysglycaemia was examined. Usual daily intake of portions of fruit and vegetables is illustrated in Figure 12, with 28.2% meeting or exceeding the 5 portions per day target. All participants reported eating at least one portion per day. There was no association between intake of fruit and vegetables and dysglycaemia (p=0.260).

Figure 12: Fruit and Vegetable Intake, 2015



Regarding exercise, almost half (46.6%) of participants were physically inactive (Figure 13). Physical activity was significantly associated with dysglycaemia ($p<0.001$) with those participants with prediabetes and T2D performing half the number of mean hours per week of activity compared to those with normoglycaemia.

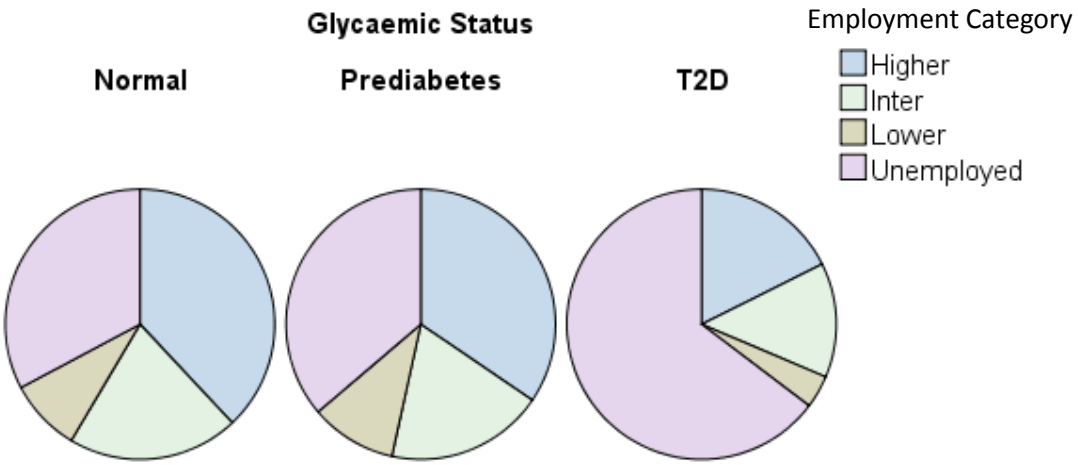
Figure 13: Physical Activity Levels 2015



Men were more likely to exercise than women: mean hours per week 3.34 (2.77-3.90) and 0.98 (0.65-1.32) respectively ($p<0.001$). Physical inactivity was correlated with age ($p=0.017$).

Given the association between socioeconomic status and diabetes in the general population, a closer examination of relationship was performed in this cohort. Three-quarters (77.2%) had achieved further education after school, 38.5% were unemployed or retired and 18.0% reported financial struggle. The relationship between National Socioeconomic Classification and glycaemic status is illustrated in Figure 14, where unemployment was significantly associated with T2D ($p=0.003$).

Figure 14: National Socioeconomic Classification by Glycaemic Status



The majority of participants with T2D were unemployed, with a relatively small proportion of those working employed in higher categories. Examination of socioeconomic status using the MacArthur UK scale corresponded with the National Socioeconomic Classification, with those with T2D categorised with a lower mean classification ($p=0.023$). However, the MacArthur Community score was statistically similar across glycaemic status groups ($p=0.736$).

For comparison data from the 2015 cohort and data from the general population in London and England as a whole (Public Health England, 2015b) are shown in Table 3.5. Although data was collected using different methodologies it appears that rates of T2D are higher than the general population, whereas rates of overweight and obesity were similar. The HIV cohort was more likely to smoke, and less likely to exercise or meet target for fruit and vegetable intake.

Table 3.5: Comparison of 2015 Cohort with General Population Data

	Prevalence		
	HIV Cohort	**London**	**England**
Type 2 Diabetes	15.1%	6.0%	6.2%
Current Smoker	21.0%	17.0%	18.0%
Inactive (Physical Activity)	46.6%	27.0%	27.7%
Meet 5-a-day Fruit and Vegetable Target	28.2%	50.5%	53.3%
Overweight or Obese	58.0%	58.4%	64.6%
Cardiovascular Disease	5.6%	2.1%	3.3%

Source: Public Health England (2015)

3.2.4 Dietary Intake, 2015

Sensitivity of Sample of Returned Diaries:

Five-day food diaries were received from 198 participants, a response rate of 58.6%. A sensitivity analysis is presented in Table 3.6. Diet diary responders were significantly older (51.7 vs 49.4 years, p=0.019). There was a trend for those with prediabetes and those of White ethnicity to be more likely to return completed diaries but these were not significant (p=0.064 and 0.078 respectively). There was also a trend for those currently experiencing financial hardship and people of Black African ethnicity not to return completed diaries, but these were not statistically significant (p=0.070 and 0.187 respectively). For all other measures the sample of participants who returned diaries was a sensitive representation of the total cohort.

Energy Balance:

Analysis of the 198 diaries is presented in Table 3.7. Mean energy intake overall was 2155 (CIs 2059-2251) kcal, with a mean of 2248 (2148-2349) kcal in men and 1806 (1571-2041) kcal in women. Mean energy expenditure was calculated to be 2130 (2087-2173) kcal overall, with a mean of 2212 (2171-2253) kcal in men and 1829 (1740-1918) kcal in women. Energy expenditure was significantly higher in those with prediabetes compared to those with normoglycaemia and T2D (p=0.016). Mean energy balance in men and women was 37 (-56 to 129) kcal and -22 (-272 to 228) kcal respectively (not significantly different by gender, p=0.594). Mean energy balance appeared to be lower for those with T2D (mean -157 kcal compared to 69 and 6 in those with normoglycaemia and prediabetes respectively). However, confidence intervals were wide and difference was not statistically significant (p=0.254).

Table 3.6: Diet Diary Sensitivity Analysis Comparing Responders with the Entire Cohort

		Diaries n=198	Total n=338	Difference *p*
GLYCAEMIC STATUS	Normoglycaemic	63.1%	67.8%	0.276[a]
	Prediabetes	23.7%	17.2%	0.064[a]
	T2D	13.1%	15.1%	0.533[a]
GENDER	Male	78.8%	74.0%	0.209[a]
AGE	Mean years	51.7	49.4	**0.019[b]**
ETHNICITY	White	57.6%	49.7%	0.078a
	Black African	26.3%	31.7%	0.187a
	Black Caribbean	8.6%	7.7%	0.713a
	Other	7.6%	10.9%	0.203a
BMI	Mean kg/m^2	27.3	27.4	0.839[b]
WAIST	Mean cm	97.2	96.9	0.798[b]
HYPERTENSION		37.4%	37.9%	0.909[a]
HDL: Triglycerides Ratio	Mean	1.48	1.39	0.440[b]
CURRENT SMOKER		19.2%	21.0%	0.615[a]
CVD		6.1%	5.6%	0.833[a]
STATIN USE		30.8%	27.2%	0.375[a]
LIPODYSTROPHY		24.2%	21.6%	0.480[a]
PHYSICAL ACTIVITY	Mean hours / week	2.81	2.72	0.814[b]
UNEMPLOYED		30.1%	29.6%	0.868[a]
RETIRED		11.1%	8.9%	0.674[a]
FURTHER EDUCATION		76.3%	77.2%	0.800[a]
FINANCIAL STRUGGLE		12.1%	18.0%	0.070[a]

NOTES Variables as defined in section 2.5.4
Responders and the entire cohort tested for significance of difference:
a Significance of difference by Chi-squared
b Significance of difference by ANOVA

Negative energy balance can be a surrogate marker for underreporting of intake as well as a true reflection of lower energy intake than expenditure. A method for calculating the level of underreporting has been devised based on the original Goldberg method, using the lower 95% confidence interval as the cut-off (Livingstone and Black, 2003). The percentage of participants with a negative energy balance below the lower 95% CI of -65.0 kcal was 46.5%. Women were more likely to underreport than men but this was not statistically significant (48.7% and 38.1% respectively, p=0.227). Black Caribbean and Black African participants were more likely to have a negative energy balance (65.4% and 76.5% respectively) compared to Whites and Others (51.8% and 46.7% respectively, p=0.019). More participants with T2D had a negative energy balance compared to those with normoglycaemia and prediabetes but this did not reach

statistical significance (69.2% compared to 56.8% and 51.1% respectively, p=0.179). The mean BMI of those reporting a negative energy balance was 28.5 kgm^2 compared to 25.6 kgm^2 in those reporting a positive balance (p<0.001). A simpler method for estimating under and over reporting has been used in the NHS Nurses study (Mendez et al., 2011). A reported mean daily intake of less than 500 kcal or more than 3,500 kcal was deemed to be unfeasible. Using this method seven participants (3.5%) would be deemed to have reported an unfeasible energy intake, with all seven exceeding a mean daily intake of 3,500 kcal.

Macronutrient Intake:

Across the cohort protein contributed a mean 18.6 ±4.9%, fat 35.5 ±6.7% and carbohydrate 46.0 ±14.5% of daily energy intake. Protein, fat and carbohydrate did not contribute significantly differently to total energy intake when compared by glycaemic status (p=0.879, 0.260 and 0.522 respectively.

Fatty Acid Intakes:

Across the cohort the mean contribution made to total daily energy intake by monounsaturated, polyunsaturated and saturated fatty acids was 12.4%, 6.3% and 12.8% respectively. There were no statistically significant differences when comparing any fatty acid group by glycaemic status, gender or ethnicity.

Sugar, Wholegrains and Fibre:

Across the cohort 40.9% of carbohydrate consumed was sugar (including milk sugar), with 22.5% of total carbohydrate intake provided by wholegrain foods. There was no statistically significant difference in either sugar or wholegrain intake between those with normoglycaemia, prediabetes or T2D.

Across the cohort mean intake of fibre, defined as non-starch polysaccharide (NSP), was 16.0 ±6.2g per day. There was no statistically significant difference in fibre intake when participants were grouped by glycaemic status, gender, ethnicity, or history of lipodystrophy.

Fruits and Vegetables:

Across the cohort the mean intake of fruits and vegetables was 1.6 and 2.2 portions per day respectively. There were statistically significant differences between groups. Those with prediabetes consumed less fruit (1.2 portions per day) than those with normoglycaemia or T2D

(1.8 and 1.6 portions respectively, p=0.009). Those with normoglycaemia consumed more vegetables (2.4 portions per day) compared to those with prediabetes and T2D (1.8 and 1.9 portions respectively, p=0.012).

Fish:

Mean intake of fish was 2.8 portions per week, with no statistically significant differences between participants grouped by gender, ethnicity or glycaemic status.

Micronutrients:

Across the cohort the mean daily intake of sodium was 2624 mg, with no statistically significant differences between participants grouped by glycaemic status. The mean daily calcium intake for the cohort was 944 mg with no statistically significant differences between participants grouped by glycaemic status. The mean iron intake for the cohort was 13.1 mg per day. Those participants with prediabetes consumed significantly more iron (15.1 mg per day) than those with normoglycaemia or T2D (12.7 and 11.4 mg respectively, p=0.010). The mean daily folate and vitamin C intakes for the cohort were 320 µg and 120 mg respectively, with no statistically significant differences for either between participants grouped by glycaemic status.

Table 3.7: Analysis of Dietary Intake by Glycaemic Status, Phenotype Study

Daily Mean (unless otherwise stated)	Normal Glycaemia		Prediabetes		Type 2 Diabetes		Total		*p*
	Mean	95% CIs	Mean	95% CIs	Mean	95% CIs	Mean	95% CIs	
Energy Intake (kcal)	2158	2029, 2287	2245	2075, 2416	1976	1719, 2232	2155	2059, 2251	0.274
Protein (% Energy)	18.7	17.8, 19.7	18.3	17.4, 19.2	18.5	16.8, 20.3	18.6	17.9, 19.3	0.879
Total Fat (% Energy)	35.3	34.3, 36.6	35.0	33.0, 37.1	37.5	35.3, 39.9	35.5	34.7, 36.6	0.260
Saturated Fat (% Energy)	12.7	12.2, 13.3	12.7	11.6, 13.7	13.5	12.1, 14.9	12.8	12.3, 13.3	0.508
MUFA (% Energy)	12.1	11.5, 12.7	13.0	12.0, 14.1	13.1	12.0, 14.3	12.4	12.0, 12.9	0.126
PUFA (% Energy)	6.1	5.7, 6.5	6.5	5.8, 7.2	6.8	5.8, 7.9	6.3	5.9, 6.6	0.290
Total carbohydrate (% Energy)	46.1	44.6, 49.7	46.2	42.3, 52.2	42.7	40.0, 47.4	46.0	44.7, 48.7	0.522
Starch (g)	143.3	132.8, 153.8	164.0	146.7, 181.3	136.0	114.3, 157.6	147.3	139.0, 155.5	0.070
Non-starch Polysaccharide (g)	16.1	14.9, 17.2	16.4	14.5, 18.3	14.5	12.7, 16.2	16.0	15.1, 16.8	0.408
Sugars (% Carbohydrate)	42.0	39.4, 44.5	39.1	31.8, 46.3	36.8	31.8, 41.7	40.9	38.8, 43.1	0.215
Wholegrains (% Carbohydrate)	22.2	18.1, 26.2	27.4	15.5, 39.4	20.7	11.9, 29.5	22.5	19.0, 25.9	0.621
Portions Fish per Week	2.8	2.2, 3.4	2.5	0.8, 4.3	2.8	1.8, 3.8	2.8	2.3, 3.3	0.922
Fruit (portions per day, mean)	1.8	1.5, 2.1	1.2	0.9, 1.4	1.6	1.1, 2.0	1.6	1.5, 1.8	**0.009**[a]
Vegetables (portions per day, mean)	2.4	2.2, 2.7	1.8	1.4, 2.2	1.9	1.6, 2.2	2.2	2.0, 2.4	**0.012**[a]
Sodium (mg)	2704	2297, 3110	2468	2184, 2752	2523	2132, 2914	2624	2356, 2892	0.741
Calcium (mg)	949	857, 1040	980	861, 1098	855	725, 985	944	878, 1009	0.546
Iron (mg)	12.7	11.8, 13.5	15.1	12.8, 17.3	11.4	10.1, 12.6	13.1	12.3, 13.8	**0.010**[a]
Folate (µg)	323	295, 350	323	287, 358	300	244, 355	320	299, 340	0.757
Vitamin C (mg)	149	118, 179	100	82, 117	110	79, 142	132	112, 152	0.091

Notes: Abbreviations: CI - Confidence Interval; MUFA - Monounsaturated Fatty Acid; PUFA - Polyunsaturated Fatty Acid
Significance calculated by ANOVA
[a]Post-hoc tests (Tukey's HSD): Fruit – Normoglycaemia different to Prediabetes, p=0.006; Vegetables – Normoglycaemia different to Prediabetes, p=0.020; Prediabetes different to both Normoglycaemia and T2D, p=0.030 and 0.017 respectively.

3.2.5 Comparison of Phenotype of Dysglycaemia, 2005 and 2015

Differences between the cohorts in 2005 and 2015 are summarised in Table 3.8. Compared to 2005, taken as a whole the 2015 cohort was older (p<0.001), heavier (p=0.019), more hypertensive (p<0.001), and had been HIV positive for longer (p<0.001). They were more likely to have been treated with ARVs (p<0.001), but had lower rates of smoking (p=0.019) and lipodystrophy (p=0.007). The 10-year CVD risk calculated by the Framingham tool and the use of statins were both significantly higher in 2015 compared to 2005 (p<0.001 for both). The prevalence of dysglycaemia was 25.9% in 2005 and 32.3% in 2015 (Figure 15). The prevalence of impaired fasting glucose excluding T2D did not differ between the cohorts (2005: 18.1 *vs* 2015: 17.2%, *p*=0.763). However, the prevalence of T2D was significantly higher in 2015 compared to 2005 (6.8 *vs* 15.1 %, *p*=0.003).

Figure 15: Prevalence of Prediabetes and T2D, 2005 and 2015

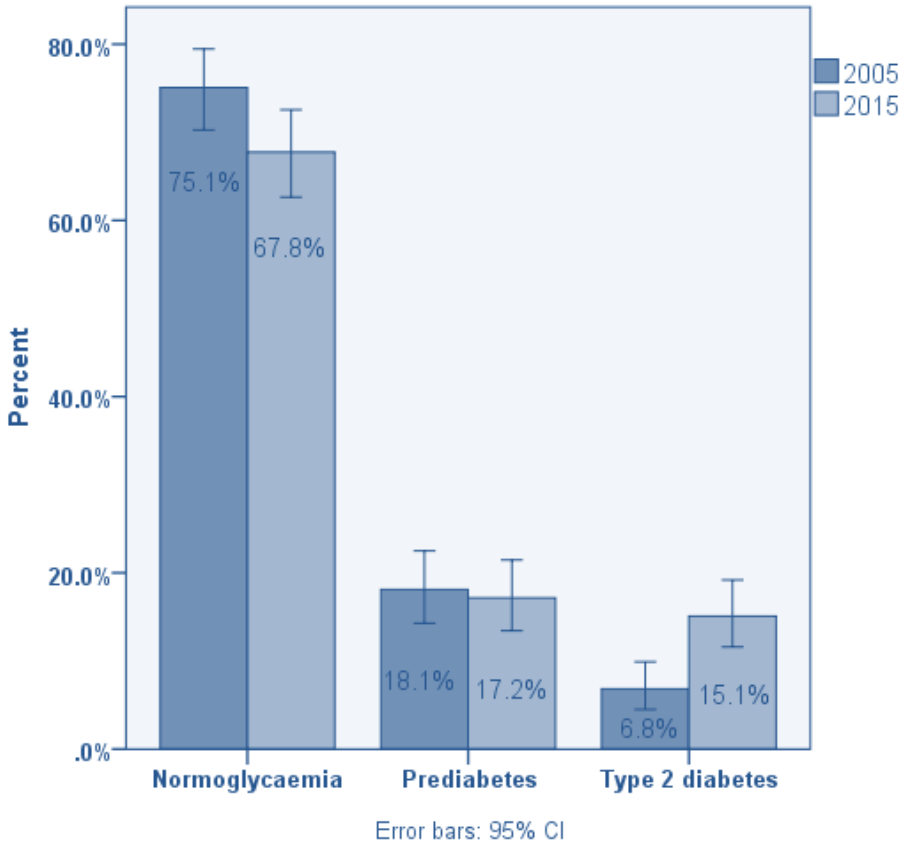


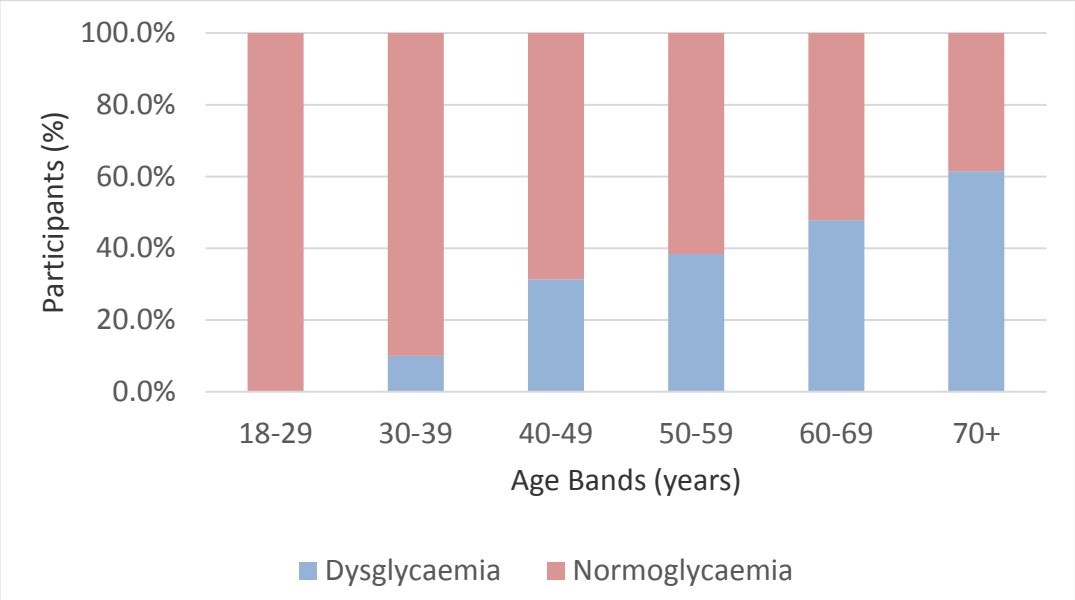
Table 3.8: Comparison of the 2005 and 2015 Cohorts

		2005	2015	*p*
NUMBER OF PARTICIPANTS		337	338	
GENDER	Male	77.2%	74.0%	0.335[a]
AGE (Years)	Median (IQR)	41 (35-47)	49 (42-57)	**<0.001[b]**
ETHNICITY	White	54.6%	49.7%	0.525[a]
	Black African	28.2%	31.7%	0.355[a]
	Black Caribbean	5.9%	7.7%	0.445[a]
	Other	11.3%	10.9%	0.903[a]
GLYCAEMIC STATUS	Normoglycaemic	75.1%	67.8%	**0.041[a]**
	Prediabetes	18.1%	17.2%	0.763[a]
	T2D	6.8%	15.1%	**0.003[a]**
BMI (kg/m^2)	Median (IQR)	24.9 (22.4-28.0)	27.4 (23.3-29.9)	**0.019[b]**
	Underweight (<18.5 kg/m2)	2.7%	2.4%	0.625[a]
	Normal (18.5-24.9 kg/m2)	49.3%	39.6%	**0.016[a]**
	Overweight (25.0-29.9 kg/m2)	32.2%	34.3%	0.683[a]
	Obese (≥30.0 kg/m2)	15.7%	23.7%	**0.009[a]**
WAIST (IDF DEFINITION)	Obese	47.7%	62.4%	**0.024[a]**
	Median cm (IQR)	91 (83-98)	95 (86-104)	0.055[b]
HYPERTENSION		19.6%	37.9%	**<0.001[a]**
LIPIDS (mmol/l)	Total Cholesterol (SD)	4.8 ±1.0	5.0 ±1.1	0.242[b]
	HDL: Triglyceride Ratio (SD)	1.59 ±1.74	1.39 ±1.19	0.180[b]
METABOLIC SYNDROME (IDF DEFINITION)		22.5%	31.8%	**<0.001[b]**
SMOKING	Current Smoker	35.6%	21.0%	**0.019[a]**
CVD (includes stroke)		2.7%	5.6%	0.055[a]
STATIN USE		16.0%	27.2%	**<0.001[a]**
% 10-YEAR CVD RISK	Mean (SD)	4.4 ±5.4	12.1 ±12.3	**<0.001[b]**
HIV Duration (Years)	Mean (SD)	6.3 ±0.9	11.6 ±0.9	**<0.001[b]**
ANTIRETROVIRAL NAÏVE		19.6%	8.0%	**<0.001[a]**
ARVs ASSOCIATED WITH T2D		23.4%	44.1%	**<0.001[a]**
LIPODYSTROPHY		27.3%	21.6%	**0.007[a]**
HEPATITIS B		4.5%	9.2%	**0.021[a]**
HEPATITIS C		3.6%	4.7%	0.433[a]

Notes:
Variables as defined in section 2.5.4
p = significance of difference between the cohorts calculated by [a] Chi-squared, [b] ANOVA;
Abbreviations: IQR – Interquartile Range; SD – Standard Deviation

To compare changes in phenotype, participants with prediabetes and T2D were combined into a single category "dysglycaemia". Factors associated with dysglycaemia are shown in Table 3.9. Those factors significantly associated with dysglycaemia at both time points included age and waist circumference (2005 and 2015, $p<0.001$), hypertension (2005 $p=0.001$ *vs* 2015 $p<0.001$), duration of HIV infection (2005 $p=0.046$ *vs* 2015 $p<0.001$) and the use of ARVs (2005 $p=0.018$ *vs* 2015 $p=0.009$). Figure 16 illustrates the association between age and dysglycaemia in 2015.

Figure 16: Distribution of Dysglycaemia by Age, 2015



Exposure to ARVs associated with diabetes and BMI were both significantly associated in 2015 only (2005 $p=0.878$ *vs* 2015 $p=0.002$, and $p=0.423$ *vs* $p=0.001$ respectively). In both 2005 and 2015 there was no association between dysglycaemia and ethnicity, gender, total cholesterol and hepatitis B or C coinfection. Factors measured only in 2015 significantly associated with dysglycaemia were hepatic steatosis, low levels of physical activity and weight gain following initiation of ARVs ($p<0.001$ for all), exposure to corticosteroid therapy (p=0.014), unemployment (p=0.003) and the National Socioeconomic Classification and MacArthur UK scales (p=0.002 and 0.022 respectively). The Macarthur UK tool asks participants to score themselves on a Likert scale comparing themselves against others across the UK whereas the Community tool asks participants to score themselves against others in their own self-defined community. In contrast to the UK scale this was not significantly associated with dysglycaemia taken as a whole (p=0.547). Similarly financial insecurity was not significantly associated with dysglycaemia (p=0.921).

Table 3.9: Univariate Analysis - Associations with Dysglycaemia, 2005 and 2015

		2005		2015	
		r	*p*	*r*	*p*
GENDER		0.02	0.721[b]	0.03	0.311[b]
AGE	Years	0.19	**<0.001[c]**	0.60	**<0.001[c]**
ETHNICITY	White	0.07	0.325[b]	0.08	0.531[b]
	Black African	0.06	0.506[b]	0.08	0.358[b]
	Black Caribbean	0.10	0.108[b]	0.06	0.253[b]
BMI[d]	Median (kg/m2)	0.04	0.423[c]	0.17	**0.001[c]**
WAIST[d]	Median	0.24	**<0.001[c]**	0.27	**<0.001[c]**
HYPERTENSION		0.02	**0.001[b]**	0.39	**<0.001[b]**
LIPIDS	Total Cholesterol	0.09	0.118[c]	0.05	0.438[c]
	HDL	0.05	0.335[c]	0.13	**0.016[c]**
	LDLa			0.10	0.072[c]
	Triglycerides[d]	0.11	**0.038[c]**	0.30	**<0.001[c]**
	HDL: Triglyceride Ratio	0.08	0.130[c]	0.27	**<0.001[c]**
METABOLIC SYNDROME		0.58	**<0.001[b]**	0.63	**<0.001[b]**
SMOKING	Current	0.01	0.716[b]	0.12	0.905[b]
CVD (excluding stroke)		0.10	0.170[b]	0.11	**0.050[b]**
STATIN USE		0.14	**0.043[b]**	0.40	**<0.001[b]**
STROKE				0.10	0.109[b]
% 10-YEAR CVD RISK	Framingham, mean	0.07	0.210[c]	0.39	**<0.001[c]**
HIV DURATION		0.11	**0.046[c]**	0.18	**<0.001[c]**
ARV NAÏVE		0.13	**0.018[b]**	0.17	**0.009[b]**
ARVs ASSOCIATED WITH DYSGLYCAEMIA		0.01	0.878[b]	0.16	**0.002[b]**
% WT GAIN AFTER INITIATION OF ARVs[a]				0.34	**<0.001[c]**
LIPODYSTROPHY		0.20	0.061[b]	0.15	**0.007[b]**
HEPATITIS B		0.01	0.873[b]	0.04	0.421[b]
HEPATITIS C		0.09	0.170[b]	0.01	0.930[b]
CD4 NADIR[a]				0.01	0.082[c]
VITAMIN D[a]				0.11	0.134[c]
HEPATIC STEATOSIS[a]				0.45	**<0.001[b]**
CHRONIC KIDNEY DISEASE[a]				0.10	0.073[b]
CORTICOSTEROID THERAPY[a]				0.14	**0.014[b]**
1st or 2nd DEGREE RELATIVE WITH T2D[a]				0.10	0.076[b]
PHYSICAL ACTIVITY[a]				0.20	**<0.001[c]**
FRUITS & VEGETABLES[a]				0.06	0.260[c]
FURTHER EDUCATION[a]				0.09	0.087[b]
SOCIOECONOMIC SCALES[a]	NSEC Mean			0.27	**0.002[c]**
	MacArthur UK Mean			0.18	**0.022[c]**
	MacArthur Community Mean			0.05	0.547[c]
EMPLOYMENT[a]	Unemployed			0.31	**0.003[b]**
FINANCIAL STRUGGLE[a]	Current			0.01	0.921[b]

NOTES: Variables as defined in section 2.5.4

Dysglycaemia - impaired fasting glucose and type 2 diabetes aggregated

[a] Data not collected in 2005; [b] Significance by Pearson Chi-squared test and Phi;

[c] Pearson correlation and significance; [d] – Non-normal distribution, data log-transformed for analysis.

NSEC – National Socioeconomic Classification

3.2.6 Statistical Modelling

Three binary logistic regression models were constructed for data from 2015 to distinguish the independent contribution of modifiable and fixed factors to dysglycaemia. Results from the three models are in Tables 3.10-3.12, with a summary presented in Table 3.13.

Collinearity was observed between the variables waist and BMI (Pearson correlation 0.851) and between HIV Duration and CD4 Nadir (Pearson correlation 0.365); the latter of each pair was excluded from regression modelling. All other Pearson correlation values were less than 0.300 and considered non-significant.

Model 1: Modifiable Factors

Model 1 included the modifiable factors hypertension, waist (cm), hepatic steatosis, HDL: triglyceride ratio and physical activity (hours per week), all of which had been demonstrated to be significantly associated with dysglycaemia in univariate analysis (see Table 3.9). The model as a whole was statistically significant (Chi-square (4, n=336) = 107.21, $p<0.001$), indicating that the model was able to distinguish dysglycaemia. The model as a whole explained between 27.3% (Cox and Snell R squared) and 38.2% (Nagelkerke R squared) of the variance in dysglycaemia and correctly classified 78.9% of cases.

As illustrated in Table 3.10 at step 1 of Model 1 the independent variable Waist no longer made a unique statistically significant contribution to the model and was removed, leaving Hypertension, Hepatic Steatosis, HDL: Triglyceride Ratio, and Physical Activity remaining statistically significant at step 2.

The strongest predictor of dysglycaemia in Model 1 was Hepatic Steatosis, recording an odds ratio (OR) of 6.738. This indicated that study participants with hepatic steatosis were almost seven times more likely to have dysglycaemia when controlling for all other factors in the model. With HDL: Triglyceride ratio, the OR of 1.562 indicated that for every whole unit increase above a ratio of 1, participants were 1.56 times more likely to have dysglycaemia when controlling for other factors. Similarly, participants with hypertension were almost 3 times more likely to have dysglycaemia. However, regarding Physical Activity, the likelihood for dysglycaemia was 0.9 times less for every extra hour per week of physical activity performed.

Table 3.10: Logistic Regression Model 1 (Modifiable Factors)

	B	Standard Error	Wald	*p*	Odds Ratio	OR 95% CIs	
						Lower	Upper
Step 1							
Hypertension	1.094	0.294	13.811	0.000	2.987	1.677	5.319
Waist (cm)	-0.004	0.011	0.159	0.690	0.996	0.974	1.017
Hepatic Steatosis	1.971	0.373	27.970	<0.001	7.175	3.457	14.892
HDL: TG Ratio	0.449	0.125	13.000	<0.001	1.567	1.227	2.000
Physical Activity (hours per week)	-0.102	0.049	4.283	0.038	0.903	0.820	0.995
Constant	-1.702	1.066	2.551	0.110	0.182		
Step 2							
Hypertension	1.073	0.289	13.749	<0.001	2.925	1.659	5.158
Hepatic Steatosis	1.908	0.336	32.163	<0.001	6.738	3.485	13.027
HDL: TG Ratio	0.446	0.124	12.887	<0.001	1.562	1.225	1.993
Physical Activity (hours per week)	-0.099	0.048	4.148	0.042	0.906	0.824	0.996
Constant	-2.112	0.296	50.786	<0.001	0.121		

Notes: n=336
Variables as defined in section 2.5.4
B – Coefficient constant (intercept); Wald – tests the significance of the coefficients

Model 2: Fixed Factors

Model 2 included the fixed factors: duration of HIV infection, weight gain following initiation of ARVs, age, exposure to ARVs associated with diabetes and lipodystrophy (historic or current), all of which had been demonstrated to be significantly associated with dysglycaemia in univariate analysis (Table 3.9). Taken as a whole model 2 was statistically significant (Chi-square (3, n=294) = 53.14, p<0.001), indicating that the model was able to distinguish dysglycaemia. The model as a whole explained between 16.5% (Cox and Snell R squared) and 22.8% (Nagelkerke R squared) of the variance in dysglycaemia and correctly classified 71.4% of cases.

As illustrated in Table 3.11 at steps 1 and 2 of Model 2 lipodystrophy and ARVs associated with dysglycaemia no longer made unique statistically significant contributions and were removed, leaving duration of HIV infection (OR 1.059), weight change following ARV initiation (OR 1.072 for every percentage point gain in weight in first year following initiation of ARVs) and age (OR 1.058 for every year) statistically significant at step 3. This model indicated that when controlling for all other factors in the model study participants were 1.07 times more likely to have dysglycaemia for each percent weight gain experienced in the year following initiation of ARVs, and 1.06 times more likely for each year of age as well as each extra year living with HIV.

Table 3.11: Logistic Regression Model 2 (Fixed Factors)

	B	Standard Error	Wald	*p*	Odds Ratio	95% CIs	
						Lower	Upper
Step 1							
Duration of HIV (years)	0.066	0.025	7.155	0.007	1.068	1.018	1.121
Wt. Gain Following ARV Initiation (%)	0.071	0.018	16.108	<0.001	1.073	1.037	1.111
Age (years)	0.056	0.014	16.184	<0.001	1.058	1.029	1.087
ARVs Associated with Diabetes	0.162	0.337	0.232	0.630	1.176	0.607	2.279
Lipodystrophy	0.074	0.357	0.043	0.836	1.076	0.535	2.166
Constant	-4.946	0.935	28.006	<0.001	0.007		
Step 2							
Duration of HIV (years)	0.064	0.023	7.538	0.006	1.067	1.019	1.117
Wt. Gain Following ARV Initiation (%)	0.071	0.018	16.117	<0.001	1.073	1.037	1.111
Age (years)	0.056	0.014	16.136	<0.001	1.057	1.029	1.087
ARVs Associated with Diabetes	0.180	0.327	0.304	0.581	1.197	0.631	2.272
Constant	-4.868	0.854	32.511	<0.001	0.008		
Step 3							
Duration of HIV	0.057	0.020	8.586	0.003	1.059	1.019	1.100
Wt. Gain Following ARV Initiation (%)	0.069	0.017	15.878	<0.001	1.072	1.036	1.109
Age (years)	0.056	0.014	16.110	<0.001	1.058	1.029	1.087
Constant	-4.680	0.779	36.055	<0.001	0.009		

Notes: n=294
Variables as defined in section 2.5.4
B – Coefficient constant (intercept); Wald – tests the significance of the coefficients

Model 3: All Factors

Model 3 included all factors from models 1 and 2. Taken as a whole model 3 was statistically significant (Chi-square (5, n=293) = 121.686, p<0.001), indicating that the model was able to distinguish dysglycaemia. The model as a whole explained between 34.0% (Cox and Snell R squared) and 47.0% (Nagelkerke R squared) of the variance in dysglycaemia, and correctly classified 81.6% of cases. As illustrated in Table 3.12, at steps 1 to 5 of model 3 lipodystrophy, ARVs associated with diabetes, waist, duration of HIV infection and physical activity were removed, leaving the following statistically significant at step 6: weight change following ARV initiation (OR 1.06 for every percentage point gain in weight in the first year following HAART

initiation), age (OR 1.07 for every year), hypertension (OR 2.58), hepatic steatosis (OR 7.29) and HDL: triglyceride ratio (OR 1.73 for each unit).

Table 3.12: Logistic Regression Model 3 (All Factors Together)

	B	Standard Error	Wald	*p*	Odds Ratio	95% CIs	
						Lower	Upper
Step 1							
Duration of HIV (years)	0.036	0.030	1.465	0.226	1.037	0.978	1.099
Wt. Gain Following ARV Initiation (%)	0.058	0.020	8.375	0.004	1.059	1.019	1.101
Age (years)	0.062	0.017	14.030	<0.001	1.064	1.030	1.100
ARVs Associated with Diabetes	0.193	0.406	0.226	0.634	1.213	0.548	2.685
Lipodystrophy	0.035	0.426	0.007	0.935	1.035	0.449	2.385
Hypertension	0.885	0.336	6.937	0.008	2.422	1.254	4.678
Waist (cm)	0.008	0.013	0.365	0.546	1.008	0.983	1.033
Hepatic Steatosis	1.761	0.435	16.384	<0.001	5.821	2.481	13.659
HDL: TG Ratio	-0.060	0.057	1.119	0.290	0.942	0.843	1.052
Physical Activity (hours per week)	0.520	0.141	13.540	<0.001	1.683	1.275	2.220
Constant	-7.057	1.684	17.550	<0.001	0.001		
Step 2							
Duration of HIV (years)	0.037	0.028	1.723	0.189	1.037	0.982	1.096
Wt. Gain Following ARV Initiation (%)	0.058	0.020	8.428	0.004	1.059	1.019	1.101
Age (years)	0.062	0.017	14.049	<0.001	1.064	1.030	1.100
ARVs Associated with Diabetes	0.183	0.387	0.224	0.636	1.201	0.562	2.565
Hypertension	0.886	0.335	6.995	0.008	2.426	1.258	4.680
Waist (cm)	0.008	0.013	0.364	0.546	1.008	0.983	1.033
Hepatic Steatosis	1.758	0.433	16.477	<0.001	5.801	2.482	13.557
HDL: TG Ratio	-0.060	0.056	1.113	0.291	0.942	0.844	1.052
Physical Activity (hours per week)	0.521	0.141	13.619	<0.001	1.684	1.277	2.221
Constant	-7.055	1.684	17.541	<0.001	0.001		
Step 3							
Duration of HIV (years)	0.030	0.023	1.587	0.208	1.030	0.984	1.079
Wt. Gain Following ARV Initiation (%)	0.056	0.019	8.203	0.004	1.057	1.018	1.099

	B	Standard Error	Wald	*p*	Odds Ratio	95% CIs	
						Lower	Upper
Age (years)	0.062	0.017	13.996	<0.001	1.064	1.030	1.100
Hypertension	0.892	0.335	7.096	0.008	2.440	1.266	4.704
Waist (cm)	0.008	0.013	0.366	0.545	1.008	0.983	1.033
Hepatic Steatosis	1.757	0.433	16.441	<0.001	5.798	2.479	13.558
HDL: TG Ratio	-0.058	0.056	1.068	0.301	0.944	0.846	1.053
Physical Activity (hours per week)	0.520	0.141	13.551	<0.001	1.681	1.275	2.217
Constant	-6.861	1.627	17.780	<0.001	0.001		
Step 4							
Duration of HIV (years)	0.027	0.023	1.399	0.237	1.028	0.982	1.075
Wt. Gain Following ARV Initiation (%)	0.055	0.019	8.123	0.004	1.057	1.017	1.098
Age (years)	0.062	0.017	13.903	<0.001	1.064	1.030	1.099
Hypertension	0.924	0.331	7.797	0.005	2.519	1.317	4.818
Hepatic Steatosis	1.871	0.391	22.872	<0.001	6.495	3.017	13.984
HDL: TG Ratio	-0.064	0.055	1.355	0.244	0.938	0.843	1.045
Physical Activity (hours per week)	0.525	0.141	13.897	<0.001	1.690	1.283	2.227
Constant	-6.097	0.999	37.219	<0.001	0.002		
Step 5							
Wt. Gain Following ARV Initiation (%)	0.054	0.019	7.807	0.005	1.055	1.016	1.095
Age (years)	0.065	0.016	15.948	<0.001	1.067	1.034	1.102
Hypertension	0.884	0.328	7.281	0.007	2.421	1.274	4.601
Hepatic Steatosis	1.970	0.382	26.561	<0.001	7.168	3.389	15.160
HDL: TG Ratio	-0.068	0.054	1.599	0.206	0.934	0.840	1.038
Physical Activity (hours per week)	0.543	0.140	15.038	<0.001	1.720	1.308	2.263
Constant	-5.902	0.968	37.142	<0.001	0.003		
Step 6							
Wt. Gain Following ARV Initiation (%)	0.057	0.019	9.016	0.003	1.059	1.020	1.099
Age (years)	0.064	0.016	15.971	<0.001	1.067	1.033	1.101
Hypertension	0.950	0.324	8.590	0.003	2.585	1.370	4.879
Hepatic Steatosis	1.985	0.380	27.260	<0.001	7.283	3.456	15.345
HDL: TG Ratio	0.547	0.139	15.488	<0.001	1.728	1.316	2.269
Constant	-6.071	0.955	40.407	<0.001	0.002		

Notes: n=293
Variables as defined in section 2.5.4
B – Coefficient constant (intercept); Wald – tests the significance of the coefficients

This final model suggests that when controlling for all other factors participants with hepatic steatosis were 7.3 times more likely to have dysglycaemia, 2.6 times more likely with hypertension, 1.7 times more likely for every unit increase in HDL: triglyceride ratio, 1.07 times more likely for each additional year of age, and 1.06 times more likely for each percent weight gain experienced in the year following initiation of ARVs.

A summary of the three logistic regression models is presented in Table 3.13. Overall the modifiable factors hepatic steatosis and hypertension contributed the largest OR when controlling for all other variables significantly associated with dysglycaemia.

Table 3.13: Summary of Logistic Regression Models

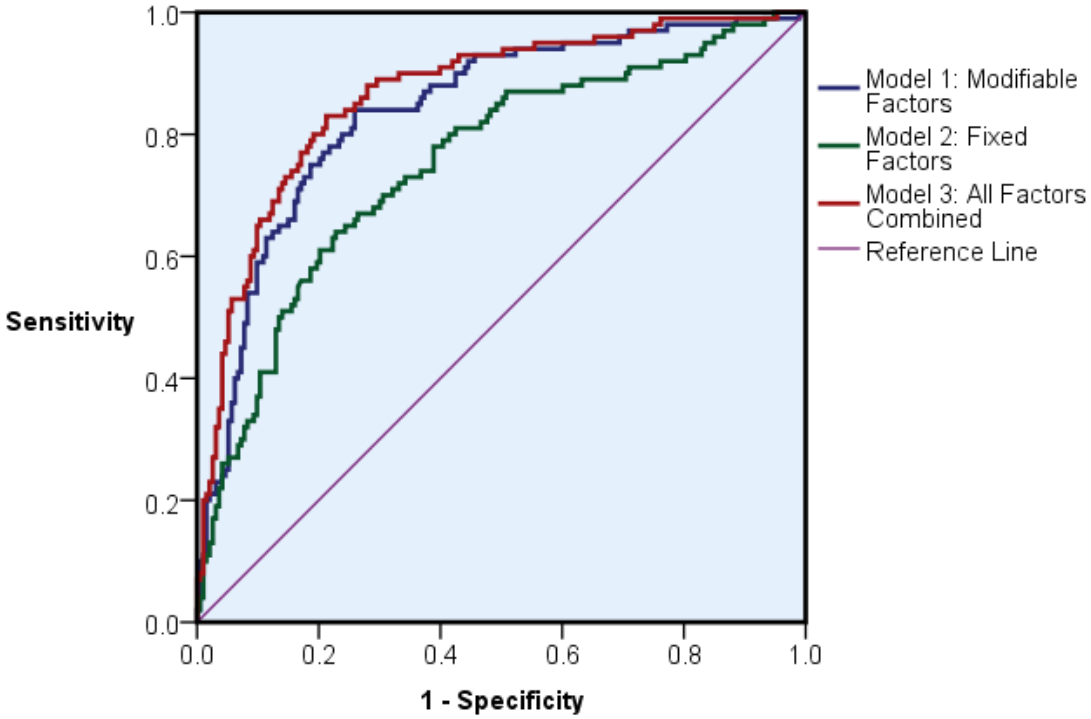
	Adjusted Odds Ratio (95% CI)					
	Model 1: Modifiable Factors	***p***	**Model 2: Fixed Factors**	***p***	**Model 3: All Factors**	***p***
Physical Activity (Hours per week)	0.91 (0.82-1.00)	0.042				
Hypertension	2.92 (1.66-5.16)	<0.001			2.58 (1.37-4.88)	0.003
Hepatic Steatosis	6.74 (3.48-13.03)	<0.001			7.28 (3.46-15.34)	<0.001
HDL: Triglyceride Ratio	1.56 (1.22-1.99)	<0.001			1.73 (1.32-2.27)	<0.001
Weight Gain Following ARV Initiation (%)			1.07 (1.04-1.11)	<0.001	1.06 (1.02-1.10)	0.003
Age (years)			1.06 (1.03-1.09)	<0.001	1.07 (1.03-1.10)	<0.001
Duration of HIV Infection (years)			1.06 (1.02-1.10)	0.003		

Note: Variables as defined in section 2.5.4

Receiver Operator Characteristic Curve Analysis:

The probability of each model predicting dysglycaemia correctly was plotted using ROC curves (Figure 17). The area under the curve (AUC) with 95% confidence intervals for each of Models 1, 2 and 3 was 0.838 (0.790-0.887), 0.752 (0.693-0.812), and 0.863 (0.818-0.908) respectively. Model 1 (Modifiable Factors) predicted dysglycaemia more efficiently than Model 2 (Fixed Factors). The difference in proportions of the AUC between Models 1 and 2 was statistically significant, calculated to be 0.086 (0.046-0.126), p=0.029.

Figure 17: Receiver Operator Characteristic Curves for Regression Models



3.2.7 Disease Risk Modelling

Cardiovascular Disease:

As described in Sections 1.8 and 2.5.5 four CVD risk prediction tools were compared for the 2015 cohort. Three were general tools: the Framingham Risk Score (FRS), QRisk2, and the Joint British Societies Score (JBS3). The fourth was the HIV-specific Data Collection on Adverse Events of Anti-HIV Drugs Study (D:A:D) risk tool. Results are described in Table 3.14. Overall, the D:A:D score attributed the lowest mean 10 year CVD risk (6.8%) compared to 7.7% for JBS3, 9.6% for QRISK2 and 12.1% for FRS. The D:A:D score classified significantly fewer participants as high risk compared to the other three models when using the threshold of 10% risk of CVD over 10 years and also the D:A:D study investigators' recommended threshold of 5% over 5 years (Petoumenos et al., 2012).

Table 3.14: Cardiovascular Disease Risk Estimation Using Four Equations

	Framingham (FRS)	QRISK2	JBS3	D:A:D
Mean 10-year Risk Score (95% CI)	12.1% (10.8-13.4)	9.6% (8.4-10.8)	7.7% (6.7-8.8)	6.8% (5.9-7.7)
High Risk Patients (>10%, 10 years)	132 (39.1%)	95 (28.1%)	77 (22.8%)	65 (19.2%)
High Risk Patients (>5%, 5 years)				69 (20.4%)

Note: Risk tools as defined in section 2.5.5

Correlation between the D:A:D risk equation and other tools is reported in Table 3.15. There was agreement in predicting between 8 and 9 out of 10 participants at high risk of developing CVD. Correlation was highest between D:A:D and QRisk2.

Table 3.15: Correlation Comparison of CVD Risk Tools

	Comparison of Risk Tools		
	D:A:D & FRS	**D:A:D & QRISK2**	**D:A:D & JBS3**
Observed Agreement of High Risk	78.4%	86.3%	89.4%
Pearson's *r* Coefficient	0.84	0.85	0.78

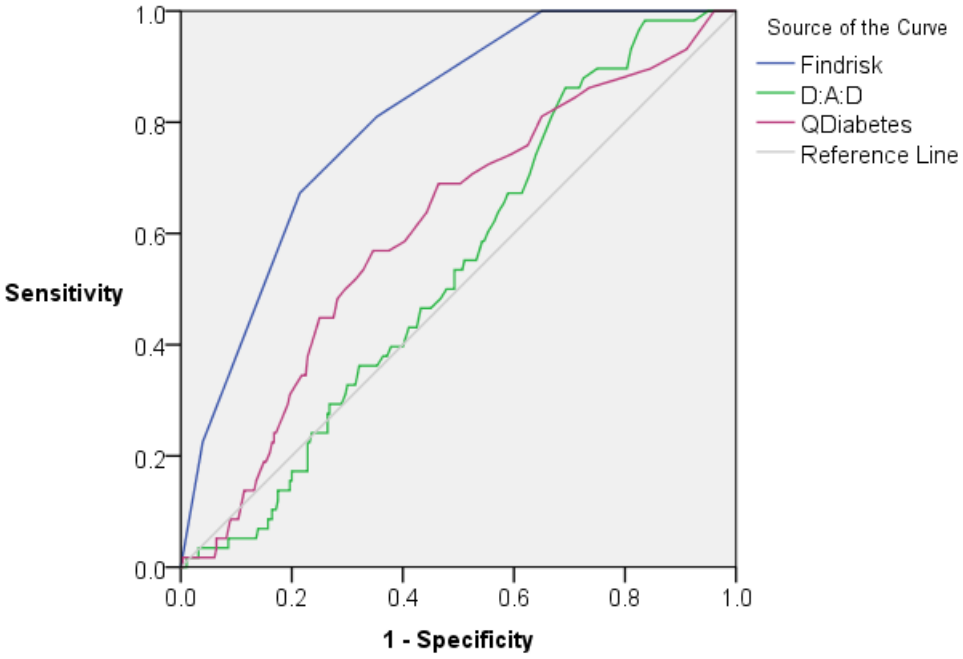
Note: Risk tools as defined in section 2.5.5

Type 2 Diabetes:

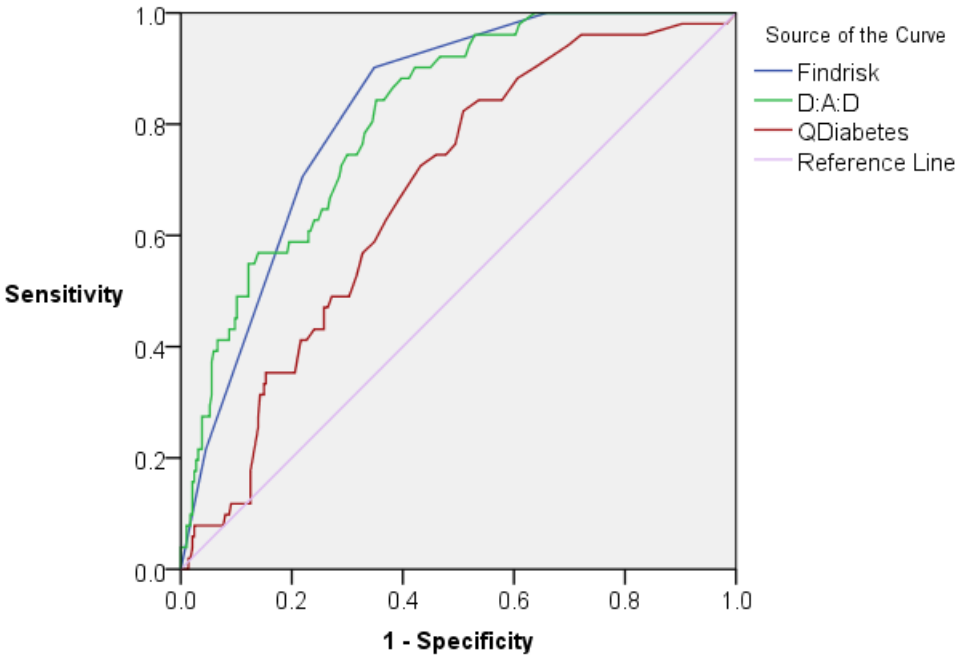
The QDiabetes tool was used to calculate relative T2D disease risk. The relative risk for this HIV cohort was 2.4 (95% CI 2.1-2.8) compared to the QDiabetes UK cohort (2.5 million patients from GP surgeries in England and Wales). Receiver Operator Characteristic curves for prediction of prediabetes and T2D (Figure 18) suggested that for prediabetes FINDRISK was the most sensitive and specific of the three tools correctly identifying 81% (AUC=0.804, 95% CI 0.751-0.858, p<0.001) compared to QDiabetes (AUC=0.611, 0.533-0.688) and D:A:D (AUC=0.540, 0.469-0.612). For prediction of T2D, FINDRISK had the greatest specificity followed by D:A:D, identifying 90% and 80% respectively (AUC=0.825; 95% CI: 0.775-0.875; p<0.001 for FINDRISC; AUC=0.814; 95% CI 0.759-0.869; p<0.001 for D:A:D). QDiabetes had a comparable specificity of 84% (AUC= 0.676; 95% CI: 0.605-0.747; p<0.001) but the poorest sensitivity of the three tools tested (42%, 65% and 66% for QDiabetes, FINDRISK and D:A:D respectively).

Figure 18: Receiver Operator Characteristic Curves for Diabetes Prediction Equations

PREDIABETES:



TYPE 2 DIABETES:



3.3 Diet and Physical Activity Intervention

3.3.1 Principal Results Summary

It was hypothesised that in people living with HIV and prediabetes a 6-month intervention of diet and physical activity advice, individualised to address ethnic and socioeconomic differences, would result in a clinically significant reduction in glucose incremental area under the curve over a three-hour meal tolerance test. Secondary objectives were to measure the change from baseline at 6 months for insulin incremental area under the curve measured in a 3-hour meal tolerance test, indices of insulin resistance/sensitivity, dietary change, physical activity, lipids, anthropometry and body composition, frailty, blood pressure, cardiovascular and diabetes risk, quality of life, bowel habits and gut symptoms.

Principal Results:

- At 6 months, the mean glucose incremental area under the curve measured in mmol per minute was 18% lower (p=0.023)
- The mean insulin incremental area under the curve measured in units per minute was 31% lower (p=0.017). Baseline fasting glucose and insulin means were significantly lower at 6 months: reductions of 6% and 24%, p=0.003 and 0.021 respectively.
- Participants achieved significant reductions in mean weight (4.6%), waist (6.2%), percentage body fat (5.9%), systolic blood pressure (7.7%), triglycerides (36.2%), 10-year cardiovascular risk (13.9%) and a significant increase in mean HDL (12.6%) and life satisfaction score (17.6%)
- Out of the 28 participants, only 6 achieved or exceeded the goal to lose 7% of body mass over the 6-month intervention period. However, the mean reduction of 4.1 kg (4.6%) was highly significant (p<0.001)
- Participants experienced significant change in diet and physical activity. There were significant reductions in mean intake of energy (20.6%), fat (14.5%), sugars (29.5%) and sodium (21.4%), and significant increases in mean total activity (52%), and intake of oily fish (47.1%), fruits (54.5%), vegetables (93.3%), wholegrains (212.9%) and fibre (37.5%).

3.3.2 Intervention Cohort Characteristics

Intervention participants ranged in age from 40-71 years (Table 3.16). Three-quarters of intervention participants were male, and all women who took part were of Black African or Caribbean ethnicities. The mean BMI was 30.7 kgm^2. Metabolic comorbidities were common. The mean duration of HIV infection was 16 years. Regarding socioeconomic status, 36% were unemployed or retired. Intervention participants (n=33) and participants with prediabetes from the phenotype study (n=58) were similar, although the intervention participants had a higher mean BMI and rate of hepatic steatosis.

Table 3.16: Intervention Cohort Characteristics

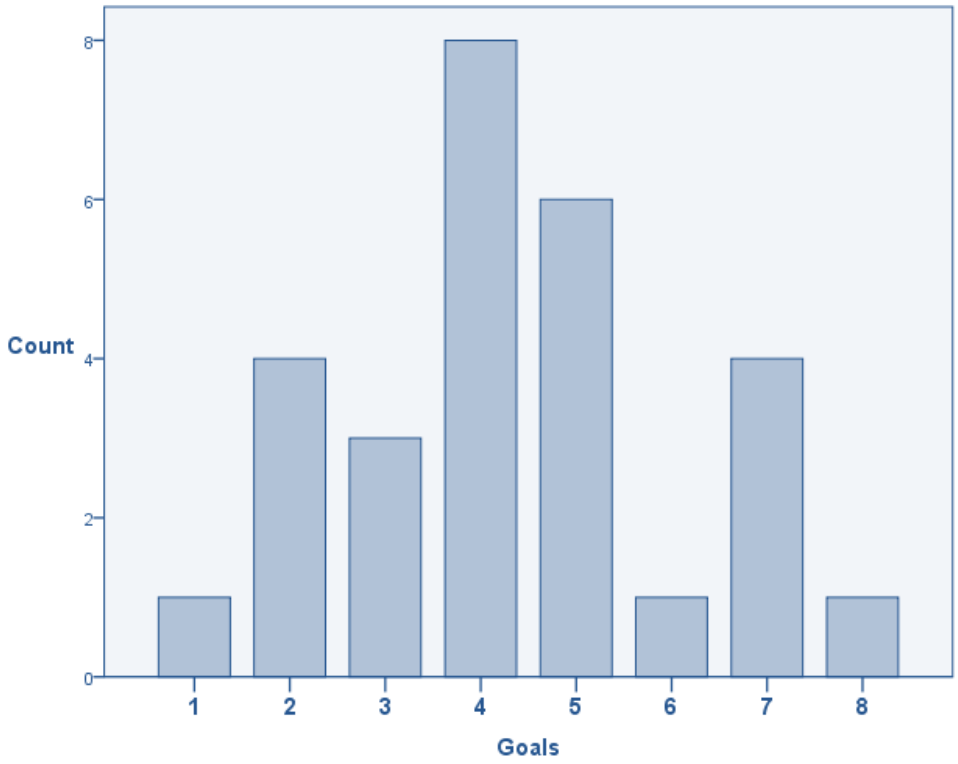
		Intervention	2015 IFG COHORT	p^1
n		33	58	
Age (years)	Mean	53.8	53.2	0.966[c]
Range		40-71	38-71	
Gender	% Male	72.7%	77.6%	0.195[b]
Ethnicity	White	57.6%	53.4%	0.080[b]
	Black African	27.3%	29.3%	
	Black Caribbean	12.1%	6.9%	
	Other	3.0%	10.3%	
BMI		30.7	28.8	**0.019[c]**
Central Obesity (IDF)		84.8%	74.1%	0.070[b]
Hypertension		60.6%	53.4%	0.450[b]
Metabolic Syndrome		78.8%	72.4%	0.268[c]
Hepatic Steatosis		63.6%	46.6%	**0.016[b]**
CVD		6.1%	8.6%	0.528[b]
Statin		51.5%	37.9%	0.068[b]
Smoker	Current	6.1%	13.8%	0.082[b]
Duration HIV Infection		15.8	13.9	0.055[c]
CD4 Nadir		195	186	0.391[c]
Duration Treated with ARVs		10.8	10.6	0.906[c]
ARVs Associated with T2D		48.5%	53.4%	0.408[b]
% Weight Gain following ARVs[a]		6.3	7.0	0.704[c]
Lipodystrophy		18.2%	24.1%	0.362[b]
Relative with T2D		57.6%	53.4%	0.450[b]
Working / Student		63.6%	63.8%	0.538[b]
Unemployed		30.3%	25.9%	
Retired		6.7%	10.3%	
Financial Struggle		9.1 %	13.8%	0.330[b]
Further Education		72.7%	75.9%	0.378[b]

Notes:
Variables as defined in section 2.5.4
Difference between intervention and all prediabetes participants (p^1)
[a] % weight gain in 12 months following initiation of ARVs; [b] Chi-square; [c] ANOVA
Abbreviations: IDF – International Diabetes Federation; IFG – Impaired Fasting Glucose

3.3.3 Participant Achievement of Diet and Physical Activity Goals

Participants were set 10 goals to achieve over the 6-month intervention (Figure 19 and Table 3.17). Achievement of 6-10 goals was considered as good adherence to the intervention, 3-5 as moderate, and achieving 2 or fewer goals considered poor. Using this criteria 22% were good achievers, 63% moderate, and 15% poor. Participants achieved a mean 4.4 goals, with men achieving 4.1 and women achieving 5.1 (p=0.185).

Figure 19: Number of the 10 Intervention Goals Achieved by Each Participant



Most participants (85%) achieved the target to reduce salt intake to less than 6g per day. The majority of participants also achieved targets to walk more than 10,000 steps per day, to reduce added sugar below 25g per day, and to reduce saturated fat intake to less than 10% of total daily energy intake (63%, 59% and 59% respectively). The most challenging goal to achieve appears to have been maintaining intake of monounsaturated fats above 15% of total daily intake. Achievement of at least 7% weight loss was met by high achievers only.

In addition to dietary goals, other changes in the nutritional composition of the diet were assessed (Table 3.18). There were significant changes in protein, fat, fibre and oily fish intake.

Table 3.17: Achievement of Intervention Goals

	% Participants Achieved Goal	No. Participants Achieving Goals		
		Poor Achievers (n=4)	Moderate Achievers (n=18)	High Achievers (n=6)
Weight Loss ≥ 7%	22%	0	0	6
Energy Deficit ≥ 600 kcal per Day	48%	1	7	5
Steps per Day ≥10,000	63%	0	11	6
Wholegrains ≥50% of Carbohydrate	41%	1	6	4
Waist: Achieve IDF Target	26%	0	7	0
Added Sugar ≤ 25g per day	59%	0	11	5
Saturated Fats ≤ 10% Total Energy	59%	1	11	4
Monounsaturates ≥15% Total Energy	15%	1	2	1
Fruits & Vegetables ≥ 7 Portions / Day	26%	0	2	5
Sodium ≤ 2.5 g per Day	85%	3	14	6

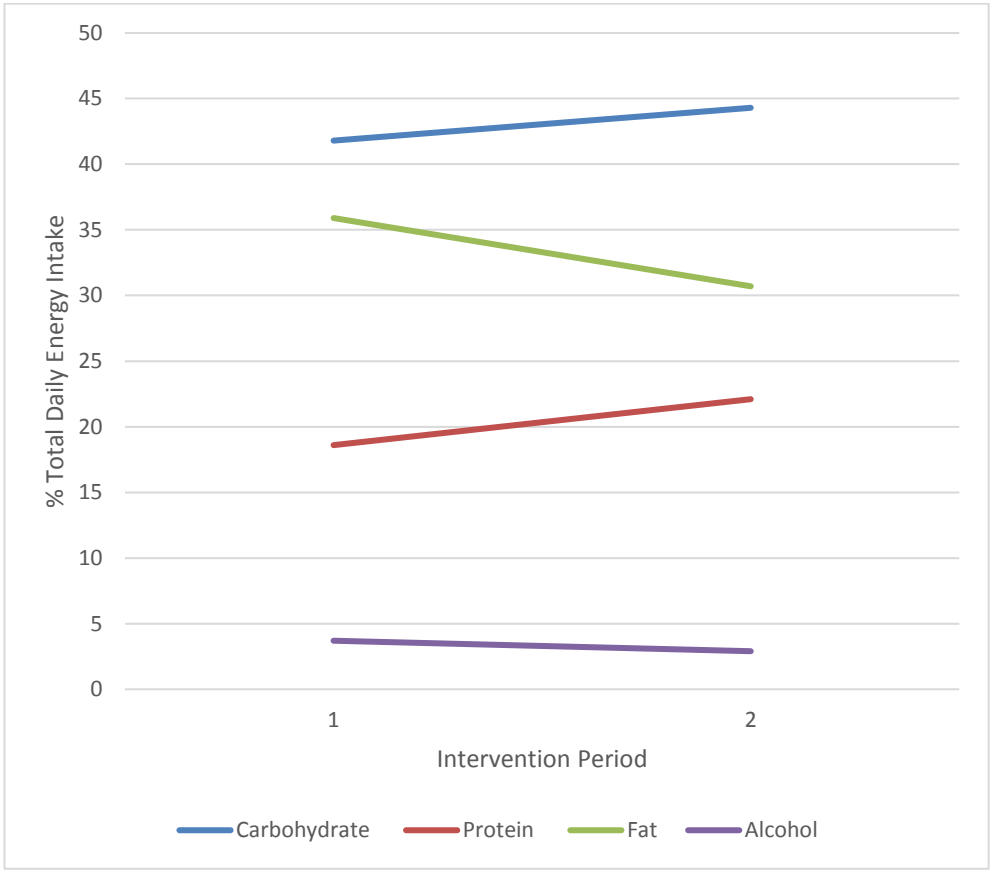
Notes: n=28
Classification of goal achievement: High – 6-10 goals, Moderate – 3-5 goals, Poor – 0-2 goals
IDF – International Diabetes Federation

Table 3.18: Intervention: Change in Dietary Intake

	Mean Baseline	Mean Endpoint	Δ Mean	95% CIs		p^a
				Lower	Upper	
Energy Intake (kcal)	2450	1946	-505	-309	-701	**<0.001**
Energy Balance (kcal)	51	-424	-475	-267	-684	**<0.001**
Carbohydrate (% TEI)	41.8	44.3	2.6	0.7	5.8	0.122
Protein (% TEI)	18.6	22.1	3.5	1.6	5.4	**<0.001**
Fat (% TEI)	35.9	30.7	-5.2	-2.1	-8.3	**0.002**
Saturated Fats (% TEI)	12.6	9.7	-2.8	-1.3	-4.4	**0.001**
Monounsaturated Fats (% TEI)	13.8	11.4	-2.4	-0.7	-4.1	**0.009**
Polyunsaturated Fats (% TEI)	6.4	6.1	-0.3	-1.1	0.5	0.474
Alcohol g	15.8	9.1	-6.7	-1.1	-14.4	0.088
Non-starch Polysaccharide g	16.6	19.5	2.9	0.3	5.4	**0.028**
Sugar g	35.2	24.8	-10.4	-1.1	-19.7	**0.029**
Wholegrains (% carbohydrate)	13.2	41.4	28.1	19.6	36.7	**<0.001**
Oily Fish (portions/week)	0.8	1.2	0.4	0.1	0.6	**0.003**
Fruit (portions/day)	1.1	1.7	0.7	0.2	1.1	**0.004**
Vegetables (portions/day)	1.5	2.9	1.4	1.1	1.8	**<0.001**
Sodium mg	2709	2128	-581	-170	-992	**0.007**
Calcium mg	1102	921	-181	10	-373	0.063
Iron mg	16.4	14.3	-2.2	1.3	-5.7	0.216

Notes: n=28
Baseline and Endpoint = Days 1 and 180 of the 180-day intervention.
[a] Paired Samples t-test for change in mean
TEI = Total Energy Intake

Figure 20: Mean Energy Intake Pre and Post Intervention



3.3.4 Primary Outcome: Changes in Glucose and Insulin

The primary outcome was 6-month change in glucose incremental area under the curve (IAUC) measured by a 3-hour frequently sampled liquid meal tolerance test, performed at baseline (Day 1) and post-intervention (Day 180). Glucose IAUC had a mean reduction of 45 mmol/l/minute (7-83 reduction, p=0.023). Insulin IAUC had a mean reduction of 4078 mIU/l/minute (797-7358 reduction, p=0.017). These reductions were equivalent to 17.6% for glucose and 31.4% for insulin. Graphs comparing mean glucose and mean insulin at time points across the 3-hour test at baseline and post-intervention are shown in Figures 21 and 22 respectively. Statistical analyses of results are presented in Table 3.19. Comparing baseline to post-intervention, there were significant reductions in fasting glucose and insulin. Fasting glucose had reduced by 0.35 mmol/l (95% CIs 0.13-0.57, p=0.003) and insulin by 3.4 units (0.5-6.2, p=0.021).

Table 3.19: Intervention: Changes in Glucose and Insulin Measures

	Mean Baseline	**Mean Endpoint**	**Δ Mean**	**Δ Mean 95% CIs**		***p*[a]**
				Lower	Upper	
Glucose (fasting)	6.04	5.68	-0.35	-0.57	-0.13	**0.003**
Glucose Maximum	8.6	8.2	-0.4	-0.9	0.1	0.114
Glucose AUC	1266	1189	-77	-143	-11	**0.024**
Glucose Incremental AUC	255	210	-45	-83	-7	**0.023**
Insulin (fasting)	14.4	11.1	-3.4	-6.2	-0.5	**0.021**
Insulin Maximum	183	117	-66	-113	-19	**0.008**
Insulin AUC	15361	11010	-4351	-7871	-831	**0.017**
Insulin Incremental AUC	12989	8911	-4078	-7358	-797	**0.017**

Notes: n=28
Measured by Frequently sampled liquid meal tolerance test, 11 samples over 3 hours
[a] Paired Samples t-test for change in mean
Glucose measured in mmol/l; insulin in international units; AUC in units x minute
AUC: Area under the curve

Comparing baseline and post-intervention, mean glucose excursions over the 180 minute test followed very similar patterns, albeit with a reduced level at each time point (Figure 21). For mean insulin early phase secretion appears very similar, with later phase secretion reduced post-intervention (Figure 22).

3.3.5 Changes in Anthropometry

Across the 6-month intervention the cohort experienced statistically significant mean reductions in all measures. Changes in anthropometry measured manually and by Bioelectric Impedance Analysis (BIA) are presented in Table 3.20. Percentage reduction in weight, waist and body fat were 4.6%, 6.2% and 5.9% respectively. The cohort also experienced a 1.7% reduction in hip size, and a 3.3% loss in lean body mass. An examination of 95% confidence intervals shows reductions for all measures at upper and lower levels, with all changes reaching statistical significance.

Table 3.20: Intervention: Changes in Anthropometry Measures

	Mean Baseline	Mean Endpoint	Δ Mean	95% Confidence Intervals		p^b
				Lower	Upper	
BMI kg/m²	30.66	29.55	-1.41	-1.87	-0.97	**<0.001**
Weight kg	88.82	84.75	-4.08	-5.41	-2.74	**<0.001**
Waist cm	107.1	100.5	-6.60	-8.37	-4.84	**<0.001**
Hips cm	107.0	105.2	-1.78	-3.05	-0.51	**0.008**
% fat[a]	29.32	27.58	-1.73	-3.01	-0.46	**0.010**
Dry muscle kg[a,c]	15.6	15.1	-0.51	-0.94	-0.09	**0.021**

Notes: n=28
[a] Measured by Bioelectrical Impedance
[b] Paired Samples t-test
[c] Equivalent to lean body mass

Figure 21: Variation in Change in Body Mass Pre and Post Intervention

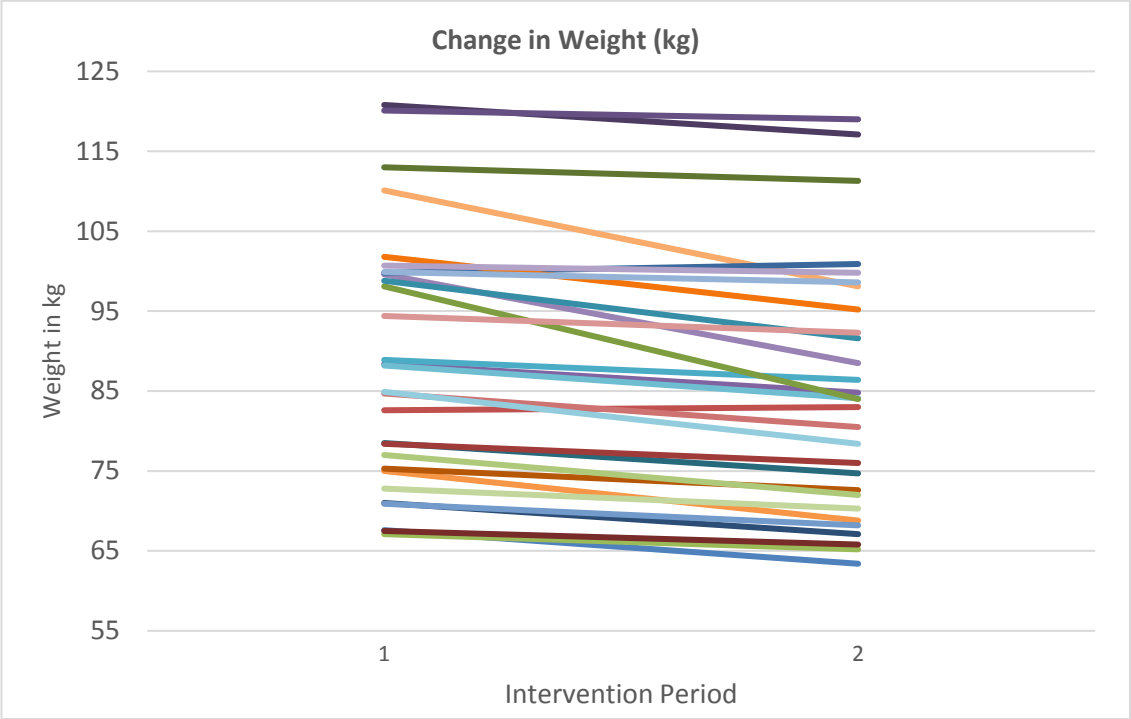
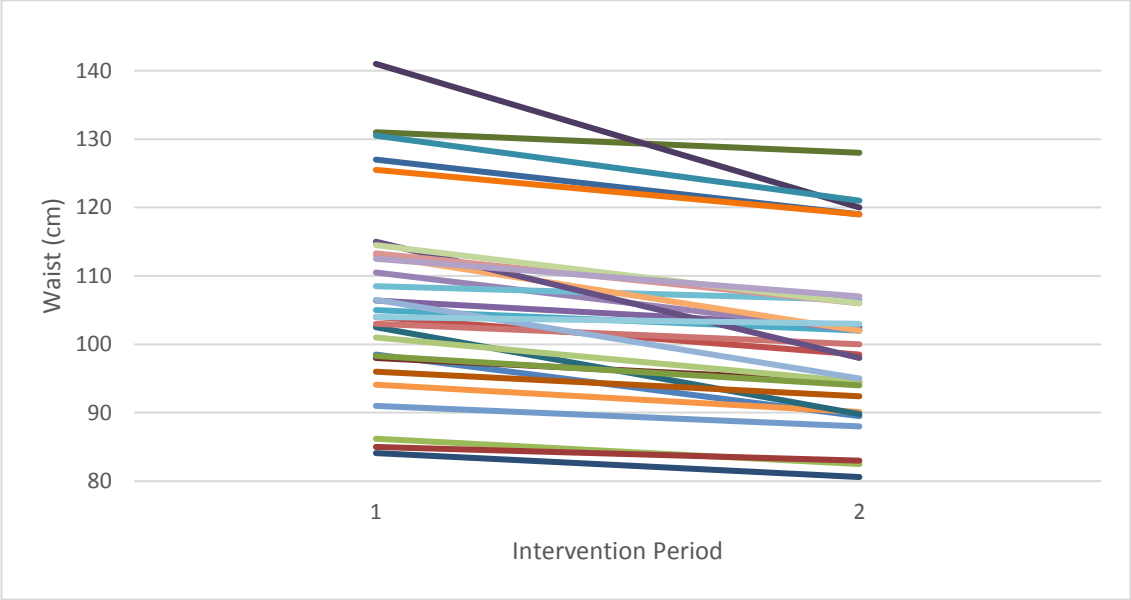


Figure 22: Variation in Change in Waist Size Pre and Post Intervention



3.3.6 Intervention: Analysis of Incretin Hormones

The incretin hormones were measured at four time points during the FSLMTT: 0, 30, 60 and 120 minutes. Mean results are presented in Table 3.21, with graphs to illustrate means

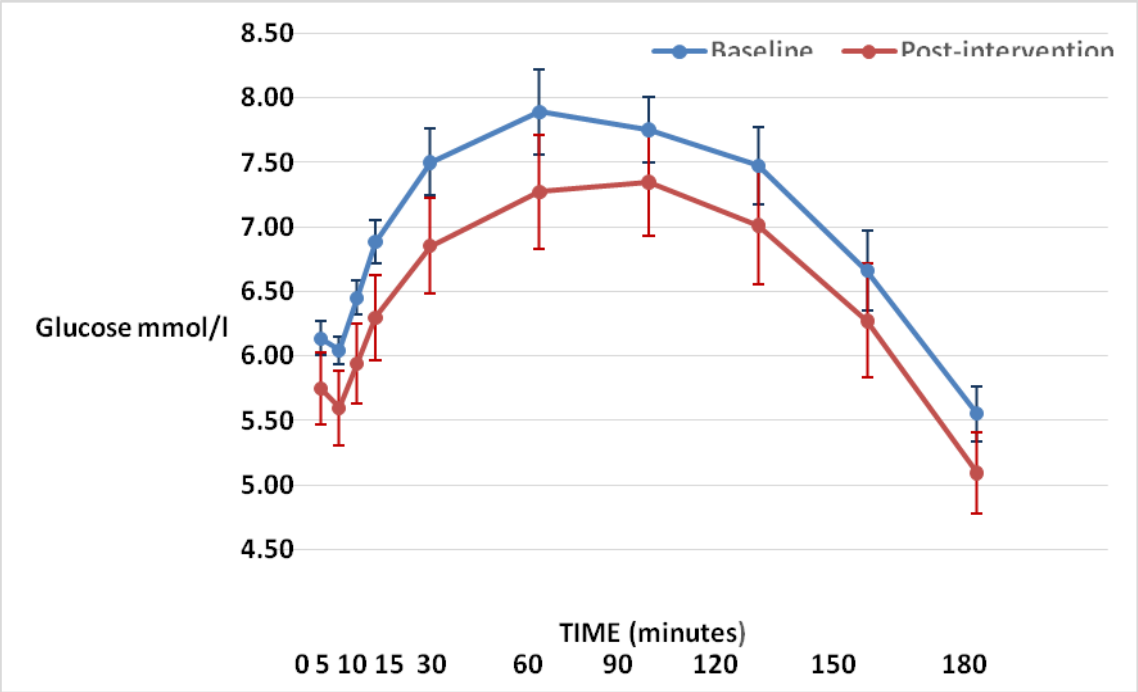
presented in Figures 23 and 24. Post-intervention there was a significant reduction of 25.1% in incremental area under the curve for GIP (mean reduction 9058 ng/l/minute, 95% CIs -15320 to -2796, p=0.006), with no statistically significant change observed for GLP-1.

Table 3.21: Effect of Intervention on Incretin Hormones

	Mean Baseline	Mean Endpoint	Δ Mean	95% CIs		p^a
				Lower	Upper	
GIP (fasting)	41.0	29.6	-11.4	-36.7	13.7	0.359
GIP AUC	40817	40584	-233	-7123	6657	0.945
GIP Incremental AUC	36078	27020	-9058	-15320	-2796	**0.006**
GLP-1 (fasting)	19.5	14.7	-4.8	-13.3	3.6	0.252
GLP-1 AUC	4146	4062	-84	-2010	1842	0.929
GLP-1 Incremental AUC	1390	1790	400	-593	1393	0.416

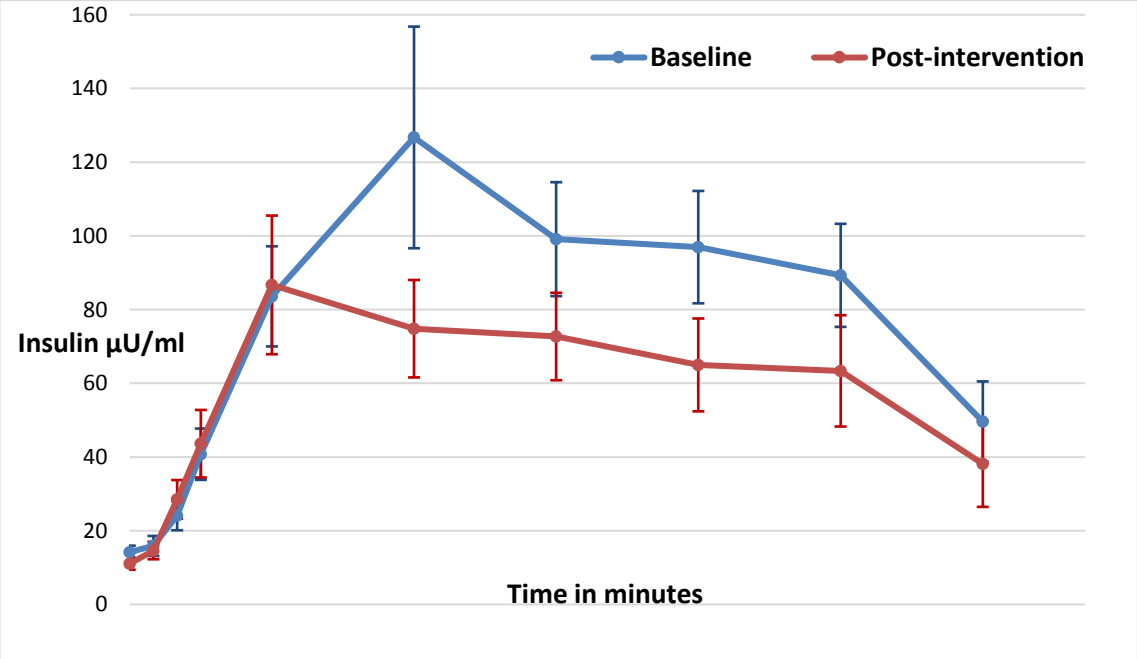
Notes: n=28
Units: GIP – ng/l; GLP-1 – pmol/l; AUC – units x minute
[a] Paired Samples t-test for change in mean
AUC: Area under the curve

Figure 23: Mean Glucose with Standard Errors, Baseline and Post-Intervention



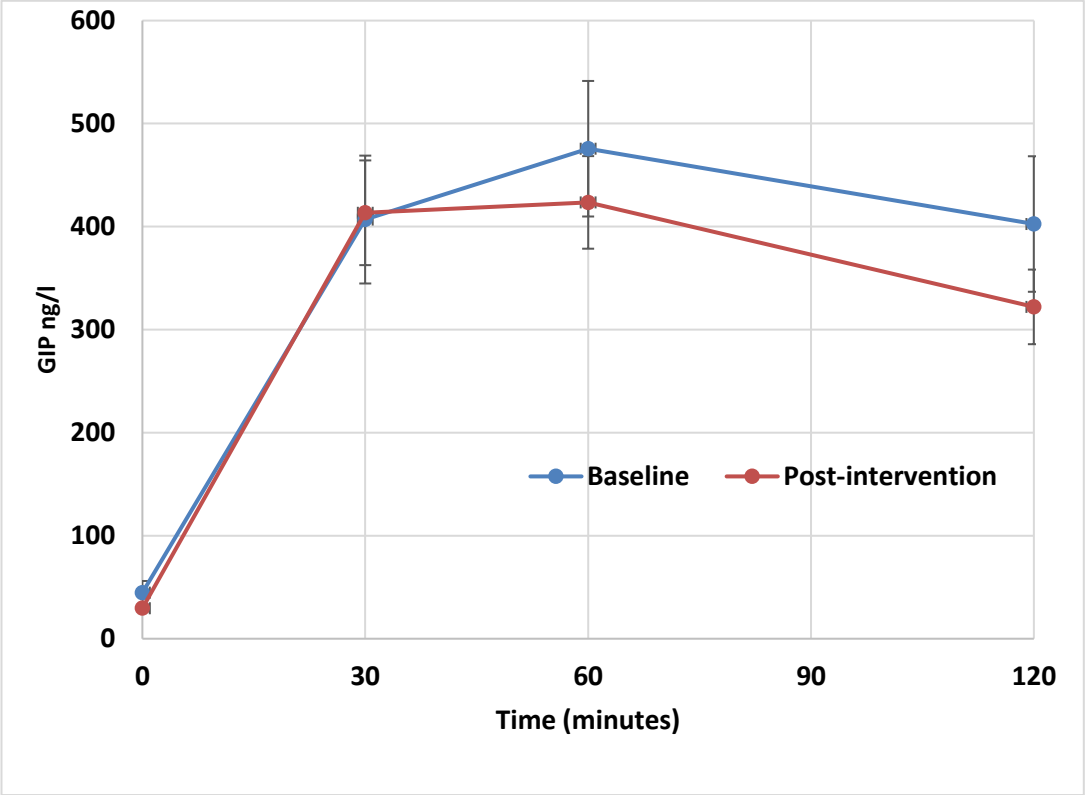
Note: n=28

Figure 24: Mean Insulin with Standard Error, Baseline and Post-Intervention



Note: n=28

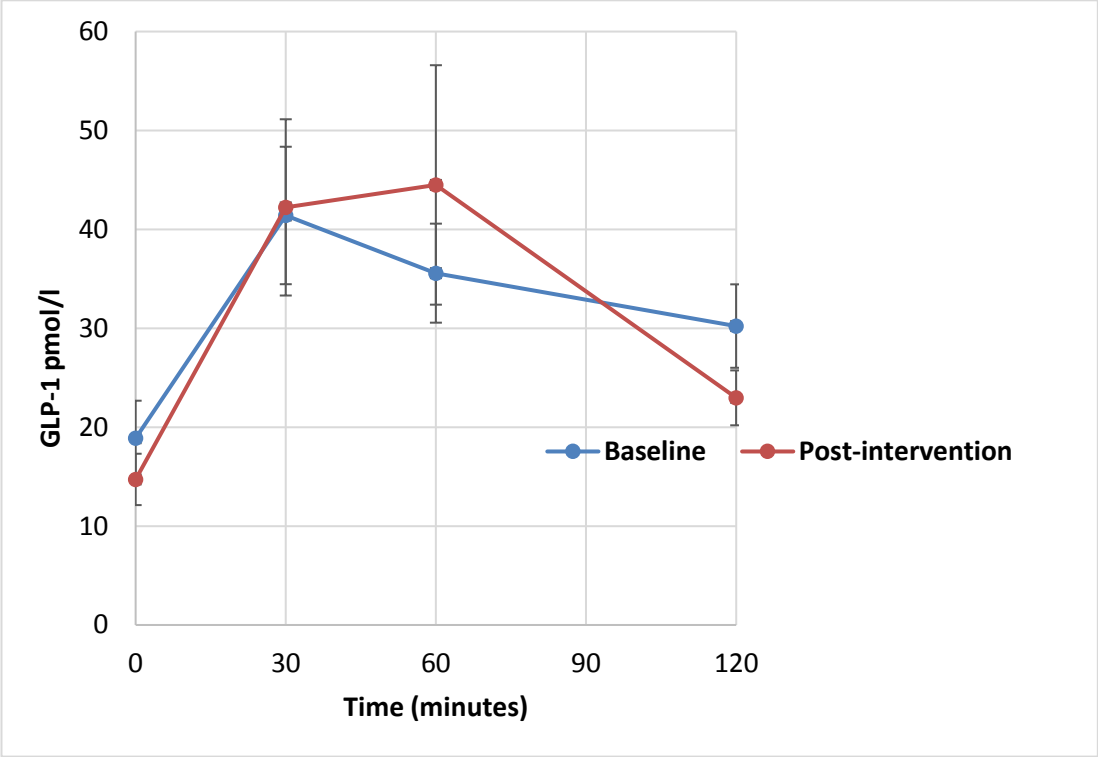
Figure 25: Effect of Intervention on Mean and Standard Error of GIP



Note: n=28

Figure 26: Effect of Intervention on Mean and Standard Error of GLP-1

Note: n=28



3.3.7 Modelling of Insulin Resistance and Glucose Disposal

Modelling of insulin resistance and glucose disposal is described in Section 2.6.6 and results are presented in Table 3.22. The intervention resulted in statistically significant improvement in insulin resistance measured by the HOMA-IR and McAuley indices, whereas the QUICKI and Matsuda indices showed trends to improvement of insulin resistance but were not statistically significant.

The baseline and post-intervention mean HOMA-IR index values remained within the range defining insulin resistance, however the mean reduction of 1.05 (CIs 0.26-1.84) was statistically significant (p=0.011). The baseline and post-intervention McAuley index were both above the threshold defining insulin resistance and post-intervention a statistically significant improvement of a mean increase of 1.40 was observed (95% CIs 0.29-2.51, p=0.016). The mean baseline QUICKI and Matsuda index levels indicated insulin resistance. Post-intervention both had mean values in the normal range suggesting resolution of insulin resistance, however the CIs were wide for both measures and the trend to improvement was not significant (p=0.088 and 0.171 respectively).

The glucose disposal rate, a measure of insulin sensitivity calculated by the Mari method (see Section 2.6.6) showed a significant improvement post-intervention compared to baseline, increasing by a mean 45 mmol/minute/m^2 (95% CIs 18-72, p=0.002).

Table 3.22: Effect of the Intervention on Modelling of Glucose and Insulin Dynamics

	Mean Baseline	Mean Endpoint	Δ Mean	95% CIs		p^a
				Lower	Upper	
HOMA-IR	3.93	2.88	-1.05	-1.84	-0.26	**0.011**
QUICKI	0.325	0.349	0.024	-0.004	0.051	0.088
MATSUDA	3.62	5.99	2.37	-1.11	5.86	0.171
McAULEY	6.08	7.48	1.40	0.29	2.51	**0.016**
OGIS (Mari)	314.7	359.6	44.9	17.8	72.0	**0.002**

Notes:
[a] Paired Samples t-test for change in mean
Insulin resistance defined as: HOMA-IR ≥2.6; QUICKI ≤0.33; Matsuda <4.3; McAuley ≤5.8
OGIS: Glucose disposal rate (Mari method), mmol/minute/m^2

3.3.8 Secondary Outcomes: Medical, Quality of Life and Activity

Medical Outcomes

Medical outcomes are presented in Table 3.23. Surrogate measures for control of HIV and strength of the immune system were unaffected by the intervention. Mean CD4 count remained constant (p=0.826). At baseline, out of the 29 participants only one had a detectable viral load and 28 were undetectable. All were undetectable post-intervention.

Both systolic and diastolic blood pressure were significantly reduced by 7.7% and 8.3% respectively (p=0.006 for both).

No statistically significant changes were noted in fasting levels of total cholesterol and LDL cholesterol although there was a trend for reduction in mean total cholesterol (p=0.155). In this cohort 51% were prescribed statins. In a sub-analysis change in LDL cholesterol was compared in those prescribed statins versus those not prescribed. There was no difference between groups using the ANOVA test (mean reduction in statin group 0.06 mmol/l, 95% CIs -0.38 to 0.26; mean reduction in non-statin group 0.08 mmol/l, 95% CIs -0.35 to 0.18; p=0.909).

Across the intervention there was a significant 36.2% reduction in mean fasting triglyceride level (mean reduction 0.75 mmol/l, 95% CIs 0.31-1.12, p=0.002) and a significant 12.6% increase in fasting HDL cholesterol (mean increase 0.16 mmol/l, 95% CIs 0.06-0.26, p=0.002).

Cardiovascular risk estimated by the QRisk2 equation saw a significant reduction (mean reduction of 1.3% in 10-year risk, 95% CIs 0.60-2.07, p=0.001). Similarly risk for type 2 diabetes saw a significant reduction (mean reduction in 10-year risk was 3.1%, 95% CIs 1.72-4.48, p<0.001).

Frailty measured by hand grip strength was statistically unchanged across the 6-month intervention. There was no change in mean frequency of opening bowels to pass stools or mean Bristol Stool Chart score (p=0.947 and 0.477 respectively). Although change in gastrointestinal symptom score was not statistically significant there was a trend for improvement in symptoms with the score reducing by 24% (p=0.062).

Table 3.23: Effect of the Intervention on Medical Outcomes

	Mean Baseline	Mean Endpoint	Δ Mean	95% CIs		p^a
				Lower	Upper	
CD4	652	662	10	-99	80	0.826
HIV Viral Load Undetectable	1	0	-1	-3	1	0.326
Systolic Blood Pressure	135.5	125.1	-10.4	-17.6	3.2	**0.006**
Diastolic Blood Pressure	81.6	74.8	-6.8	-11.5	2.2	**0.006**
Total Cholesterol	4.88	4.72	-0.17	-0.40	0.07	0.155
LDL Cholesterol	2.78	2.70	-0.07	-0.27	0.12	0.429
HDL Cholesterol	1.27	1.43	0.16	0.06	0.26	**0.002**
Triglycerides	2.07	1.31	0.75	-1.12	-0.31	**0.002**
10-year CVD Risk % (QRisk2)	9.59	8.27	-1.33	-2.07	-0.60	**0.001**
10-year Diabetes Risk % (QD)	17.2	14.1	-3.1	-4.48	-1.72	**<0.001**
Frailty (Grip Strength)	34.4	35.0	0.6	-1.9	3.1	0.602
Frequency open bowels / day	1.6	1.6	0.0	-0.2	0.2	0.974
Bristol Stool Chart Score	3.6	3.8	0.2	-0.4	0.8	0.477
Gastrointestinal Symptom Score	7.6	5.8	-1.8	-3.6	0.1	0.062

Notes:
HIV Viral Load: Expressed as number undetectable out of total cohort of 29 participants
QD: QDiabetes risk equation; 10-year CVD and Diabetes risk controlled for age
Blood pressure – units of mm Hg; Lipids – mmol/l; Grip Strength – kg; Bristol Stool Chart – mean score from 1-7 scale; gastrointestinal symptom score – mean score on scale 0 (no symptoms) – 33 (maximum possible).
[a] Paired Samples t-test for change in mean

Table 3.24: Effect of the Intervention on Quality of Life

	Mean Baseline	Mean Endpoint	Δ Mean	95% CIs		p^a
				Lower	Upper	
Satisfaction with Life	64.8	76.2	11.4	4.0	18.8	**0.004**
Health Concerns	89.4	89.8	0.4	-4.2	5.0	0.855
Financial Concerns	75.4	75.8	0.3	-6.8	7.4	0.929
HIV Medication Concerns	86.9	91.4	4.5	1.0	8.0	**0.014**
Mastery of Living with HIV	90.5	89.3	-1.2	-7.6	5.3	0.720
HIV Disclosure Concerns	62.0	69.0	7.0	-3.0	17.0	0.164
Relationship with Doctors	72.3	80.2	7.8	-5.1	20.8	0.225
Sexual Functioning	54.4	61.6	7.2	-5.1	19.5	0.240
Overall Quality of Life	75.3	80.5	5.2	-0.2	10.7	0.060

Notes:
Measured by the HIV-specific HAT-QoL instrument
Scores are expressed as percentage, where 100% is the highest possible quality of life. For example a higher Financial Concerns score equates to fewer concerns
[a] Paired Samples t-test for change in mean

Quality of Life Outcomes

Quality of life was measured using the HIV-specific HAT-QoL instrument (Table 3.24). Each component was scored as a percentage where 100% is equivalent to the highest possible quality of life. The change in mean overall quality of life score showed a trend for improvement over the 6-month intervention (increase of 5.2%, 95% CIs -0.2 to 10.7, p=0.060). Of the individual components of the instrument, the intervention had the greatest impact on the mean score for life satisfaction (increase of 11.4%, 95% CIs 4.0-18.8, p=0.004). The intervention also had a statistically significant effect on concerns about HIV medicines (fewer concerns post-intervention) but not on any other factor. There were no statistically significant correlations between individual or combined quality of life measures and achievement of intervention goals.

Physical Activity Outcomes

In addition to steps per day measured by pedometer (results presented in Table 3.17) physical activity was also measured using the International Physical Activity Questionnaire (IPAQ) with results presented in Table 3.25. Although a reduction in sedentary time was observed across the intervention, this was not statistically significant (p=0.217). The intervention increased time spent walking and performing intense activities (mean increase 53%, p=0.015, and 213%, p=0.022 respectively) but changes in moderate activities were not statistically significant (p=0.450). Metabolic equivalents (METs) were calculated with the change in mean total value being highly significant with an increase of 52% (95% CIs 29-76%, p<0.001).

Table 3.25: Effect of the Intervention on Physical Activity

		Mean Baseline	Mean Endpoint	Δ Mean	95% CIs		p^a
					Lower	Upper	
Sedentary	(minutes)	462	411	-51	-132	31	0.217
Walking	(minutes)	517	789	273	57	488	**0.015**
Moderate Activity	(minutes)	351	413	62	-104	227	0.450
Intense Activity	(minutes)	37	116	79	12	146	**0.022**
Walking	(MET mins)	1705	2605	900	189	1611	**0.015**
Moderate Activity	(MET mins)	1403	1650	248	-414	909	0.450
Intense Activity	(MET mins)	297	931	634	99	1170	**0.022**
Total Activity	(MET mins)	3405	5186	1782	989	2575	**<0.001**

Notes:
Measured by the International Physical Activity Questionnaire
Scores are expressed in minutes per week. MET=Metabolic equivalent
[a] Paired Samples t-test for change in mean

3.4 Qualitative Investigation

3.4.1 Principal Results Summary

Twenty-three participants consented to be interviewed, 19 who took part in the pilot intervention, and 4 who declined to take part. Analysis of interviews identified key themes of confidentiality and fear of disclosure of HIV status. Those who declined participation or achieved fewer intervention goals exhibited an external health locus of control, blaming diabetes risk on HIV medicines. Those who achieved more goals considered prediabetes treatable. Enablers included a desire to avoid adding to pill or disease burden, and a strong support network. Deliberate weight loss leading to loss of cultural identity and disclosure of HIV status were significant barriers. Participants found the intervention largely acceptable. They suggested that future interventions should offer a range of methods of support and consider logistics of research appointments.

3.4.2 Sampling and Cohort Characteristics

As described in Section 3.1.3, a total of 44 out of 55 participants screened to have prediabetes and treated with antiretroviral medicines were invited to interview. Of these 44, 23 (52%) consented to be interviewed, 19 who took part in the intervention and 4 who declined to take part in the intervention.

Women were more challenging to recruit to interview whether they declined to take part or took part in the intervention. As shown in Figure 10, 22 participants with prediabetes did not meet inclusion criteria or declined to take part in the intervention and all were invited to interview. Of these 22, 13 were male and 9 female. None of the 9 women consented to be interviewed whereas 4 of the 13 men agreed to take part. Additionally, of the 9 women who took part in the intervention, 5 agreed to be interviewed and 4 declined. All of the men taking part in the intervention who were invited to interview agreed to take part.

Both participants diagnosed with T2D at baseline of the intervention and withdrawn at that stage consented to be interviewed. Two further participants dropped out of the intervention. One consented to be interviewed and the second declined further contact on dropping out.

The demographic of the interview cohort is described in Table 3.26. Although disproportionately male, the group interviewed otherwise represented the demographic of the larger cohort. The mean age of those interviewed was not significantly different to the mean age of those with prediabetes from the larger phenotype study presented in Section 3.2.3 (54.6 and 53.3 years respectively, p=0.110).

Most interviewees had been diagnosed with HIV and treated with anti-HIV medication for a considerable length of time (mean duration 15.6 and 11.8 years respectively) although a range was represented.

Table 3.26: Cohort Characteristics of Interviewees

		Gender		Total
		Male	Female	
Participation Status (n)	Declined Intervention	4	0	4
	Completed Intervention	11	5	16
	Withdrawn (Diabetes Diagnosis)	2	0	2
	Dropped Out of Intervention	1	0	1
	Total	*18*	*5*	*23*
Age (years)	Range	40-71	42-58	40-71
	Mean	56.5	49.7	54.6
Ethnicity (n)	White	13	0	13
	Black African	2	5	7
	Black Caribbean	2	0	2
	Other	1	0	1
Employment Status (n)	Working	7	4	11
	Unemployed	3	1	4
	Retired	8	0	8
Sexuality (n)	Heterosexual	7	4	11
	Gay	9	0	9
	Not disclosed	2	1	3
Years Since HIV Diagnosis	Mean	15.5	16.0	15.6
	Range	3-28	10-22	3-28
Years of Treatment with ARVs	Mean	11.4	13.5	11.8
	Range	3-19	10-18	3-19

3.4.3 Interviews

All participants were offered a choice of interviewer, either myself or one of the Health Advisers (trained counsellors) from the HIV clinic. Interviews were conducted at a place and time to suit the participant. Venues offered included the participant's own home or workplace, a meeting room in a non-clinical area of St. Thomas' Hospital, an interview room in the Clinical Research Facility at St. Thomas' Hospital or a consultation room at the charity Terence Higgins Trust near King's Cross in London. All 23 participants interviewed chose me to conduct the interview. Two participants requested to be interviewed at home, and one at their workplace. Of the remainder, nine chose to be interviewed in a non-clinical room at St. Thomas' Hospital and eleven at the Clinical Research Facility.

All 23 interviews were conducted with only the interviewer and interviewee present and in a private location where security of confidentiality was assured. Interview number 21 conducted at the participant's home was briefly disrupted by the behaviour of the participant's dog, with the interview and recording paused for four minutes and restarted. This disruption did not affect the overall quality of the interview. All other interviews progressed without interruption. The mean duration of interviews was 44 minutes. Interview number 1, essentially a pilot, lasted for 21 minutes. Interview number 20 was also brief, lasting 20 minutes. The participant was unexpectedly called to work shortly before the interview began and the interview could not be rearranged. Topics for discussion were prioritised by the interviewer. The duration of interviews other than numbers 1 and 20 ranged from 28 to 84 minutes. No repeat interviews were conducted.

3.4.4 Development in Framework Analysis

The initial framework construct for analysing interview data was based on the three topic guides developed (Appendix 7.7). The topic guides divided the flow of the interviews through a general introduction, attitudes to being diagnosed with dysglycaemia, participation in this study, enablers and barriers to change, design of the study, and finally attitudes to research participation in general. The initial Framework coding tree (Table 3.27) was tested at Interview 1, and although the Framework continued to employ these initial primary nodes, further nodes were added or developed in an iterative fashion as new themes were observed as interviews progressed.

Following interview 2, a code was added regarding attitudes to body shape prior to the intervention and for those who had dropped out or completed the intervention, current body shape. Analysis following interview 4 suggested that support was a key element in behaviour change in this cohort and was separated from other elements and added as an independent code.

The final novel code added at interview 21 was regarding gay men who self-identify as 'bears'. This theme is explored fully in Section 3.4.8. As an introduction, the bear community is a sub-section of gay men who reject normative idealised male lean muscularity, and are more likely to be hairier, heavier and more masculine (as defined below, with images of men who self-identify as bears in Appendix 7.9) than mainstream gay men (Moskowitz et al., 2013). To quote interviewee 23:

> "In terms of masculinity [being a bear is…] more about a rejection of what would be considered the traditional kind of gay attributes or qualities. There is a kind of appreciation of people with big bellies and that broad look and with the beards and all that kind of stuff, and obviously there's the beer drinking as well, the culture of that". [Interviewee No. 23, male, aged 41].

Table 3.27: Interviews: Initial Coding Tree in Framework Analysis (Added to Subsequently)

Interview Section	Primary Analysis Code	Secondary Analysis Code
Introduction	General Health Living with HIV - diagnosis	Comorbidities Current attitudes
	Current Behaviours	Diet Physical Activity
Attitudes to Diagnosis of Prediabetes or Type 2 Diabetes	Living with prediabetes or T2D	Reaction to diagnosis Beliefs about diabetes
	HIV and Diabetes Together	Opportunities Concerns
Taking Part in this Study	Enablers Barriers	
Lifestyle Change	Enablers	Knowledge Facilitators Motivation
	Barriers	Social Physical Motivation
Intervention Design	Acceptable Aspects Less Acceptable Aspects Suggestions for Future Design	
Research Participation	HIV Research General Research	

3.4.5 Purposive Sampling

The preliminary design purposively sampled participants to include maximum diversity:

- Gay men who exercise
- Gay men with a higher BMI
- Black African-origin men and women
- Those who withdrew from the intervention
- Those who were eligible but declined to take part in the intervention

Preliminary thematic analysis following interview 11 suggested no new significant data was emerging from interviews with White male participants who had achieved most targets during the 6-month intervention. From this point, only those White males who had achieved fewer targets were invited to interview; six White male participants who performed well in the intervention were not invited to interview. New data continued to emerge from analysis of interviews with non-White participants and invitation to interview for this group continued. Data saturation was achieved for White male participants only.

3.4.6 Thematic Analysis

Development of themes for analysis progressed (Table 3.28 to Table 3.35) resulting in an expansion of themes from 21 to a total of 76 themed codes and sub-codes arranged as separate columns within the Framework. On receipt of each interview transcription, coding was completed systematically with references placed in each cell within the Framework. With all 23 interviews completed, the grid now had data coded and distributed between 1748 cells. Empty cells were noted as absence of a theme was considered potentially significant.

Table 3.28: Interview Analysis: Development of Introductory Themes

General Health	Comorbidities Mental Health Attitude to Life
Living with HIV	Optimistic Approaches Concerns and worries Disclosure Medication Issues
Current Diet Behaviours	Perception of behaviours
Current Physical Activity Behaviours	Perception of behaviours

Table 3.29: Interview Analysis: Development of Diagnosis Themes

Living with Prediabetes	Reaction to diagnosis Concerns / worries Optimism
Diagnosis of Type 2 Diabetes	Reaction to diagnosis Concerns / worries Optimism Pragmatism
Diabetes and HIV	Implications of comorbidity Concerns / worries Disclosure Medication Issues

Table 3.30: Interview Analysis: Development of Body Image Themes

General Body Image	Acceptance or positive views Unhappiness with body image HIV-specific
African Attitudes	General HIV-specific Changing Attitudes
Gay Male Body Image	General HIV-specific

Table 3.31: Interview Analysis: Development of Lifestyle Themes

Behaviour Examples	Healthier Less Healthy	
Capability to change, e.g. knowledge	Enablers	General HIV-specific
	Barriers	General HIV-specific
Opportunity to change, e.g. physical activity incorporated into work routine	Enablers	General HIV-specific
	Barriers	General HIV-specific
Motivation to change, e.g. peer support	Enablers	General HIV-specific
	Barriers	General HIV-specific

Table 3.32: Interview Analysis: Development of Support Themes

Support	Types of support received Participation with Others Active Support from Others Lack of Support from Others
Isolation	Seeking Support to Circumvent Isolation Opposition from Others Physical Isolation Social Isolation

Table 3.33: Interview Analysis: Development of Bear Themes

Bear Identity	Definitions Culture
Health Implications	Body Image Bear-specific Barriers Peer Pressure

Table 3.34: Interview Analysis: Development of Intervention Design Themes (Process Analysis)

Recruitment	Advertising Methods of contact
Logistics	Clinical Research Facility Duration of Intervention
Measurement of Primary Outcome	Attitudes to FSLMTT
Support	Frequency of review Flexibility of appointments
Participant Information	Appreciative opinion Critical opinion
Future Design	New technologies Delivery

Table 3.35: Interview Analysis: Development of Research Participation Themes

Participation in this Intervention	Motivations to participate Barriers to participation Confidentiality / Disclosure
HIV-specific Research	History of participation Motivation to participate Barriers to participation Confidentiality / Disclosure
Research Participation in General	History of participation in non-HIV research Attitudes to research in general Motivation when not HIV-related Barriers when not HIV-related

3.4.7 Health Issues

General Health:

During the introductory phase of the interview participants were asked broad questions regarding their general health. Participants volunteering positive examples of general health experiences projected a sense of optimism during the interview. Interviews with those participants who focused on negative health experiences were characterised by a sense of pessimism. Having a positive outlook on life reflected acceptance of health issues:

> "I'm quite enjoying my life. I'm not going to break down and cry about [*health issues*], I mean I've got them. You live with them". [Interviewee No. 12, male, aged 63].

A prevalent theme was negative experience of multiple morbidities and health challenges other than HIV. These included arthritis, liver disorders, chronic fatigue, cancer, cardiovascular disease, hypertension, chronic pain and vulnerable or chronically poor mental health. Participants reported struggling to cope with multiple comorbidities:

> "I get a lot of pain in my back, I'm blind in my left eye, and in my right eye I'm now getting intermittent loss of vision every now and again. And that's worrying me". [Interviewee No. 2, male, aged 64].

> "Your mental health does have a knock-on effect with everything, whether it be anxiety or depression, whatever it is you're suffering from at the time. So that's a big obstacle to get over – with me it is". [Interviewee No. 3, male, aged 44].

Living with HIV:

Participants discussed both positive and negative impacts of being diagnosed and living with HIV. Acceptance of HIV and rationalisation of the condition as a controlled, quiescent infection was associated with a positive attitude:

> "HIV seems to be under control, so no worries there. It's just very, very routine and uh, not a problem". [Interviewee No. 17, male, aged 67].

> "I've lived with HIV for a long time now and each extra year I live is a bonus". [Interviewee No. 21, male, aged 59].

> "Now [*HIV is undetectable*] I can do so many things". [Interviewee No. 8, female, aged 48].

Others were resigned to the HIV diagnosis but mentioned associated health implications including pill burden and social concerns:

> "Having lived with the HIV and obviously [*the HIV medicines are*] keeping me alive, but I do feel that my quality of life has deteriorated". [Interviewee No. 7, female, aged 49].

Prevalent themes were negative aspects of being diagnosed and living with HIV:

> "HIV is my worst nightmare". [Interviewee No. 13, male, aged 40].

> "You meet someone, a boyfriend or whatever. You mention I'm HIV positive, you start seeing them distancing themselves and whatever it is you think is going to happen, they leave and it's really sad". [Interviewee No. 15, female, aged 42].

The health burden of living with HIV was commonly mentioned. This included chronic medication side effects including lipodystrophy, changes in skin pigmentation, gastrointestinal problems, and the legacy of HIV and opportunistic infections, including peripheral neuropathy, scarring, blindness and arthropathy.

Denial of HIV infection was mentioned as a coping strategy:

> "I'm not thinking of HIV at all. I don't have it. That is the attitude which I've got. I didn't think about it because I don't have it". [Interviewee No. 14, female, aged 51].

> "HIV denial is common among us African people". [Interviewee No. 4, female, aged 55].

HIV stigma and fear of disclosure of HIV status was a prevalent concern:

> "People they think you are bad, you've maybe been sleeping around but as I told you before, how I got HIV, I found out I was positive, there was only one partner that I had, and I knew straight away where I got my sickness from. People they sort of discriminate against you". [Interviewee No. 7, female, aged 49].

> "I think the biggest thing for me is disclosure – I have an issue with that. I've had bad experiences with it". [Interviewee No. 23, male, aged 41].

Diagnosis of Prediabetes:

Almost all participants in both the intervention and interviews were diagnosed with prediabetes less than three months prior to participation in this research programme. Thematic analysis of reaction to the prediabetes diagnosis indicated polarity of response. Interviewees with a more optimistic response to the diagnosis were characterised by surprise but resignation or by lack of surprise and acceptance of the diagnosis. These participants discussed the potential reversibility of the condition:

> "So I was surprised to hear that [*prediabetes diagnosis*] and at the same time not that surprised because the thing runs in the family". [Interviewee No. 8, female, aged 48].

> "Not exceptionally concerned no, because as far as I was concerned, something like that you can deal with by checking your diet and exercise". [Interviewee No. 11, male, aged 63].

Participants with a negative reaction to the diagnosis commonly blamed the HIV medications for developing prediabetes. Others blamed poor diet or increasing obesity, alone or in combination with medication, with one participant expressing embodiment of feelings:

> "What made me borderline? HIV medication and cakes". [Interviewee No. 1, male, aged 71].

> "I tend a bit to blame the drugs more than dietary and hereditary factors". [Interviewee No. 22, male, aged 46].

> "I was horrified, a bit outraged actually. How dare my body betray me like this". [Interviewee No. 9, male, aged 60].

Those with a negative reaction to the diagnosis of prediabetes mentioned the fear of progression to type 2 diabetes itself. Participants talked about direct observation of diabetes-related morbidity and mortality, where family members and friends experienced loss of vision, amputation and premature death. Participants also talked about the diagnosis of prediabetes adding to the burden of multiple health concerns.

> "I've got so many health issues, getting other bad news about my health, I don't feel good". [Interviewee No. 6, male, aged 40].

Diagnosis of Type 2 Diabetes:

Those participants who were diagnosed with T2D itself discussed the impact this had on their lives. As with those diagnosed with prediabetes, adding to disease and pill burden were common themes:

> "I'll be given a bottle of metformin and I'll have to add that to my pill burden, it'll be another thing". [Interviewee No. 22, male, aged 46].

> "I've got HIV, I've got bone problems, and now this diabetes so I might not last long. It's like too much weight for one body. I have HIV but I'll live until maybe 60 years. But now I've reduced it to 55. So I felt bad. I sat down and cried, honestly". [Interviewee No. 7, female, aged 49].

However reactions to the diabetes diagnosis ranged from this extreme of fearing reduced life expectancy to lack of understanding and denial:

> "I think I asked you, does that mean I've got to start injecting myself? And of course when you said probably not yet well I though that's alright, it's not serious". [Interviewee No. 12, male, aged 63].

HIV and Diabetes Together:

Participants discussed their fear of potential for interaction between both HIV and T2D diseases and between their respective medications:

> "I don't really know if one will react with the other in any way". [Interviewee No. 16, male, aged 71].

> "Taking HIV *and* diabetes medicines, so it would be very hard, yeah". [Interviewee No. 8, female, aged 48].

There was discussion at length regarding which of the two conditions was worse, with a spectrum of views from one condition being much more serious than the other or both being of equal consequence and burden. Those participants who believed HIV was worse than diabetes talked about HIV-related illness they had experienced. One participant talked at

length about his HIV-related kidney disease and how for him this was much more of a health priority than diabetes. Interviewees mentioned management of diabetes through diet and exercise whereas HIV required daily medication and was potentially transmissible:

> "Diabetes is not as life-threatening as HIV. Diabetes is a disease but I know it can be easily tackled with food without taking any medicine. But HIV is not like that, no". [Interviewee No 16, male, aged 71].

The relative ease and difficulty of disclosing diagnosis of diabetes and HIV was introduced. One participant described how she would not be fearful of telling friends about diabetes as no-one would potentially link this with HIV. Another explained that he had truncated the title of the research study from "STOP Diabetes in HIV" to "STOP Diabetes":

> "I told them I was part of a research thing called Stop Diabetes and you had identified it through my blood, but not that it was linked with HIV. I don't tell anyone about that at all". [Interviewee No. 11, male, aged 63].

In addition to those who had experienced significant diabetes-related morbidity and mortality among family members, diabetes was thought to be worse than HIV by those who had not themselves experienced significant HIV-related disease burden:

> "For me, I think diabetes is probably worse actually. For me, because I've been lucky with my HIV that it hasn't made me ill". [Participant No. 18, male, aged 45].

3.4.8 Body Image

African Body Image:

African women who participated in both the phenotype and intervention studies had a higher mean BMI than participants of other ethnicities. Interviewees discussed the acceptability and social valorisation of larger body sizes among African people. They suggested that in women, malnutrition is equated with infertility and conversely overweight and obesity is associated with the opposite. In African men larger body sizes were thought to be associated with wealth.

Changing attitudes among second generation Africans in the UK were mentioned, where pressure to achieve a lower BMI was thought to be more prevalent. Peer pressure among African women was mentioned, where during an open discussion about reducing diabetes risk deliberate weight loss was discouraged:

> "I said 'Oh look how big I am'. They said, 'Oh no, no, no, you're not big, that is the right thing, the good right thing'. I said, 'I need to lose weight'. They said, 'no, no, no, don't lose weight'". [Interviewee No. 14, female, aged 51].

The association of thinness with AIDS among African people was an issue. One participant told a story about her church congregation in the UK, largely of African origin, where a member who was rapidly losing weight was wrongly assumed to be ill with AIDS and subsequently isolated socially. Social pressure to remain overweight to mask HIV infection was discussed by all women interviewees of African-origin:

> "But if you're big, people will think, oh you're normal because you're big. Yeah, with African women some wants to be big you know like, especially if you are HIV positive". [Interviewee No. 4, female, aged 55].

Body Image Among Gay Men:

Gay male participants reported pressure to achieve a perceived ideal of a lean muscular body:

> "Well, I looked at myself side on in the mirror and I thought would you sleep with you and I thought no I wouldn't".

Not all participants in the intervention were overweight. Those participants with the lowest BMIs were gay men who had been living with HIV for many years, exposed to more metabolically toxic medications in the past. Development of dysglycaemia was problematic for those with lower BMIs who expressed a sense of unfairness that this had happened to them when diabetes is largely associated with obesity. Wasting and lipodystrophy were discussed and although participants had been living with a self-assessed suboptimal BMI for many years, they had not come to terms with this and discussed continuing efforts to gain weight:

> "I don't want to keep get thinner and thinner – I strive to put on as much weight as I can. But what can I do not to lose weight, and at the same time decreasing my sugar intake?" [Interviewee No. 1, male, aged 71].

> "...what I wanted to do was to work on that and to build up my muscles and things like that". [Interviewee No. 10, male, aged 44].

Gay Men Who Identify as Bears:

The sub-section of gay men who reject normative idealised male lean muscularity and adopt a hairier, heavier, masculine appearance self-identify as bears (Appendix 7.9). The bear community within the gay scene was presented as a supportive non-judgemental environment. Participants reported a fun, beer-drinking community, contrasting this with the lean body-beautiful aesthetic they felt was predominant among other gay men:

> "I like to go to a bear pub where I know a lot of people and they're nice people. I've never been short of people who are attracted to me or think I'm attractive. And so I suppose you get a lot of your confidence from that. My partner likes me being a bigger guy, yeah". [Interviewee No. 23, male, aged 41].

> "My ex said I was a fake gay man because I didn't do like the things gay men are supposed to do like go to the gym". [Interviewee No. 22, male, aged 46].

A diversity of people was described within the bear culture, with varying body shapes and levels of fitness. Participants who identified as bears vocalised a tension between remaining overweight to be part of the group whilst acknowledging the health risks that brings:

> "I mean everyone's still different even when you're within a group [*bears*]. I think you've got some extremes where people are into really big guys and also like feeding and that kind of thing. I have one friend who's into really big guys, a lot bigger than me, and he says he has a moral issue with his preference but also the fact that he knows that people are not healthy when they're that big". [Interviewee No. 23, male, aged 41].

Remaining immersed within bear culture was seen as a risk for body dysmorphia, where continual positive acceptance of being obese was resulting in a loss of perspective. Deliberate weight loss, although acknowledged to be healthy, was described negatively, as a loss:

> "Losing weight would take away their bearness. Being a bear is like a licence to be fat". [Interviewee No. 22, aged 46].

HIV-related Body Image Issues

Weight gain following initiation of ARVs was an issue for interviewees, with obvious and excessive weight gain readily associated with medication commonly mentioned:

> "The weight gain was almost immediately coinciding with the drug, the protease inhibitor regime, especially the central weight gain". [Interviewee No. 22, male, aged 46].

> "Being big is one thing every woman doesn't like. I wasn't even happy about my size because all along I've been someone who was small". [Interviewee No. 7, female, aged 49].

> "I have a problem because of the medication I'm taking which makes me put on weight… because I know my HIV contribute to my weight". [Interviewee No. 6, male, aged 40].

Weight loss, deliberate or unplanned, was reported as problematic. For some interviewees this was an HIV-related concern but not for others:

> "For example, if I lose weight, get very small and even if I wasn't HIV positive, the first thing they will point at, that one has got AIDS. Because of the weight you have lost". [Interviewee No. 7, female, aged 49].

> "Friends hadn't seen me for about 4 or 5 months, I said to them 'can you notice any difference in me?' and they said yes your face looks much thinner, you've lost weight. And I said 'oh yeah I'm on a special diet for blah blah blah'. I thought, I knew exactly what they were thinking – am I going full blown with AIDS?" [Interviewee No. 2, aged 64].

> "People thinking I was positive because of this weight loss? No. That never crosses my mind. People, people ask me if I have cancer". [Interviewee No. 10, male, aged 44].

Body shape changes as a legacy of lipodystrophy were a concern. Central fat accumulation was associated with development of diabetes risk:

> "Well borderline diabetes was a shock to start with but it was something I expected because I've been on medication for the last seventeen years and my body kept on changing. I used to get big on the upper part of my body. Normally kept getting big and getting smaller on the bottom part of my body". [Interviewee No. 18, male, aged 45].

> "Yeah, the fat thing's horrible cos you don't want to wear a tight T shirt. It's embarrassing when you go swimming because it stands out as a fat lump". [Interviewee No. 18, male, aged 45].

> "The HIV medicines. One, my stomach. Some people suspect, every time I go to the gym people think I'm pregnant. So that was another problem. In fact, one time I was travelling and some lady told me, oh are you going to maternity, antenatal clinic?" [Interviewee No. 4, female, aged 55].

3.4.9 Enablers and Barriers to Behaviour Change

Enablers and barriers to behaviour change are categorised using the Theoretical Domains Framework and COM-B (Michie et al., 2011b, Cane et al., 2012), summarised in Figure 26.

Knowledge

Interviewees valued improved knowledge as an enabler to behaviour change. Understanding of the importance of good nutrition and regular exercise, healthy and less healthy behaviours, and a better understanding of diabetes risk were all highlighted:

> "We now always try and buy the low calorie, low fat foods, all the spreads are the low fat ones". [Interviewee No. 13, male, aged 40].

> "I'm very fond of herring, so one tells oneself it's terribly good for one but not when it's, you know, sizzling away in butter. In winter time I used to like putting a mutton curry together and thinking oh gosh I'm being terribly authentic because I'm using ghee but now I know ghee is basically butter". [Interviewee No. 9, male, aged 60].

Conflicting advice from health professionals and from the media, for example advising to take medications or products that would have no benefit or potentially an adverse effect, negatively impacted on gain in knowledge:

> "The pharmacist he said [*to help lose weight*] if I'm drinking water he told me add sodium bicarbonate. I should try and put at least a spoon and drink it". [Interviewee No. 7, female, aged 49].

> "There are too many conflicting evidences about this and that out there. I think a lot of people are not too sure. I was drinking loads of Lucozade. I thought you had bad sugars and good sugars so I thought glucose was OK". [Interviewee No. 19, male, aged 57].

Participants discussed knowledge of sustainability of behaviour change, commenting that drastic changes and traditional weight loss diets are unlikely to be sustainable. This increase in efficacy was attributed to maintaining focus across the intervention.

Skills

Participants discussed new or enhanced skills as enablers to behaviour change, for example improved understanding of nutritional information on food packaging and planning skills.

Social Role and Identity

Adopting unfamiliar food habits and eating unfamiliar foods were mentioned as both enablers and barriers to change, with participants embracing or avoiding the unfamiliar.

> "Where I come from our diet is based on carbohydrates which is, there is a lot of sugar in it. So that is the main food that we have. If I'm not eating that, what else can I eat?" [Interviewee No. 8, female, age 48].

> "African food doesn't taste nice without salt and oil". [Interviewee No. 4, female, aged 55].

Isolation or the need for peer support as barriers to change were sufficient to discourage participation in the intervention. Overcoming isolation facilitated success:

> "I always wanted to go to the gym but was lazy or always want company. I didn't have the motivation to go by myself". [Interviewee No. 8, female, aged 48].

Self-identifying as part of a group and normalising the inevitability of obesity was a barrier to change:

> "I'm at that sort of age where you get a gut anyway. You know, I don't see it as being a big deal". [Interviewee No. 12, aged 63].

Beliefs, Capabilities and Self-confidence

Barriers within this domain were HIV-specific whereas enablers were general in nature. Enablers included understanding that change may be difficult at first but that persistence delivers results, with success sustaining progress. Interviewees felt that the intervention would improve overall health, not just prevent diabetes, and found this motivating. Belief that food can act as a health enabler was mentioned as an enabler by one participant:

> "OK I would say food is a medicine. Before if I eat vegetables, if I don't eat vegetables, it doesn't matter. All I knew of is weight. People tell you this or that thing makes you put on weight. But this six months, I've realised that your eating habits also really help in my so many sicknesses, something like that, yeah helps fight diseases for you". [Interviewee No. 7, female, aged 49].

In terms of barriers, participants with HIV-related illness such as peripheral neuropathy were not used to doing physical activity:

> "I started one session but I was sick, I have joint pain because I'm not exercising for years. So with the job I can't cope with that so I stop". [Interviewee No. 6, male, aged 40].

Participants reported not being able to invest in lifestyle change, believing this was futile given the legacy of HIV infection and ARV side effects:

> "I really thought it was just like as you get older and you're on these drugs, this [*diabetes*] is just going to happen. There's nothing you can do. You can try to be healthy but you're not going to avoid it, it's just going to happen. So I actually thought I'd probably just go on metformin. I was like, you know, let's treat it medically, it's time". [Interviewee No. 22, male, aged 46].

Participants with lower BMIs felt that with HIV-related weight loss the intervention was personally less relevant. Lipodystrophy was cited as a barrier to exercising, with interviewees expressing embarrassment about their body shape.

Optimism

Optimism was associated with enablement to lifestyle change. Interviewees talked about enjoying changing eating behaviours, interest in trying new or different foods or enjoying the challenge of trying out different methods of physical activity. Pleasure was expressed regarding eating healthier foods. Optimism was associated with resilience in the intervention:

> "And so there is a feeling that I should um you know, take this opportunity. So when you told me that on the phone [*about prediabetes*] I was surprised but then I was thinking, oh well actually this is good I can do something". [Interviewee No. 22, male, aged 46].

Beliefs about Consequences and Outcomes

Although the intervention was designed to reduce diabetes risk it could have a positive impact on a wider range of health issues. This was an enabler to change for participants with comorbidities. The desire to prevent diabetes was a motivator, particularly for those who had observed diabetes-related morbidity or mortality among friends or family members. The recognition that progression to diabetes was not inevitable and that lifestyle change could reduce risk was described as a powerful motivator:

> "It doesn't just get rid of a fat belly um it actually is good for the heart and I think it might be good for one mentally as well". [Interviewee No. 9, aged 60].

> "You know, I want to control it before I get to a stage where I have to take insulin or something". [Interviewee No. 15, aged 42].

> "You can't do anything about HIV, you can't take the blood off from your body and get new blood. But with diabetic, you can avoid it". [Interviewee No. 14, aged 51].

An HIV-related enabler was avoiding the consequence of adding to pill burden through development of diabetes. This was clearly a powerful emotional issue for interviewees:

> "To have to start diabetes medicine as well, on top of the HIV ones. And I thought that is going to be like very hard. And it was hard for me as well to be on the HIV one because I'm not used of taking medicine as well. And like to take everything every day, regularly, is very hard. Yeah, so if I would have like gone over, my sugar level was high and I am diabetic, I have to take that one, I don't know, maybe regularly as well it would have been very hard, yeah and it would have been very hard". [Interviewee No. 8, female, aged 48].

Similarly concerns about disclosure of HIV status through deliberate weight loss were sufficiently powerful to lead to declining to participate in the intervention. Additionally, weight loss was believed to indicate AIDS-related wasting. The strength of emotion regarding this was sufficient to lead to the desire to reverse successful loss of weight on exiting the 6-month intervention:

> Interviewer: "You said that you were happy that you were reducing your risk of diabetes, is that right?"
>
> Interviewee: "Right, but I wasn't happy with the effect on my face. I'd rather have diabetes and a full face. Because you have to have fillers that need to be done every month, and eventually you got to pay for them and they're not cheap. So I'd rather be a diabetic injecting myself every day, than look like I look now."

> Interviewer: "How do you feel about how you look now?"
>
> Interviewee: "Shit. I look in the mirror! I see a gaunt looking face that I didn't have before I started this."
>
> Interviewer: "Ok, what are you going to do over the next few months now you've finished?"
>
> Interviewee: "Eat as much crap as I can to put weight on. I ate 2 boxes of Maltesers last night." [Interviewee No. 2, male, aged 64].

Reinforcement, Incentives and Punishment

Enablers within these domains were general and not HIV-specific. Participants found ways round their perception that healthier food and exercising were both financially prohibitive.

New approaches to shopping, cooking and exercising were reported as less expensive, and an incentive to continue with the intervention:

> "I stopped driving, that's the first thing. I stopped driving everywhere, cos I was walking. So I saved money on the fuel. That's the first thing that sort of like balanced out the expense of the fruit and veg initially. And afterwards, I discovered that if I go to the fruit and vegetable markets, on the Sunday, I can buy the fruits and vegetables I need for the week. I can buy at probably a third of the price in the supermarket". [Interviewee No. 15, female, aged 42].

For those who were relatively isolated, frequent contact with health professionals was an enabler to ongoing participation. Exercising was a means to increase social interaction as well as improving mental health:

> "So that come in handy, the exercise and, and talking to people. Because it helps me a lot when I get out and talk". [Interviewee No. 10, male, aged 44].

An emotionally strong enabler was the desire to get back into shape, particularly for those who were previously fit. A practical incentive to achieve pedometer step goals was the realisation that during the London rush hour it is often quicker to walk than take public transport:

> "You know, I would have just jumped on the bus. But now I don't mind walking back and forth to the station, it's not that far. It's quicker and I quite enjoy it. Walking you see a lot more as well". [Interviewee No. 16, male, aged 71].

Intentions

Within this domain enablers to change included commitment to succeed during the intervention as participants who had not performed well during the first three months wanted to know if they had developed type 2 diabetes. There was also a desire in general to tackle obesity. The link between obesity, diabetes and reduced life expectancy had been made and participants expressed the desire to live longer to see their grandchildren grow up.

Barriers to participation and changing behaviour included a general lack of commitment and lack of willpower. Participants recognised that behaviours needed to change and that diabetes was preventable but acknowledged that they were not ready to change at this time.

Goals

The intervention was designed with 10 goals to achieve. This was appreciated by participants, particularly those with mental health challenges and those with physical disability:

> "The motivation is the scheme – having goals set is really important". [Interviewee No. 3, male, aged 44].
>
> "I was guilty of the sin of pride achieving daily goals. I was guilty of the sin of pride when my waist got smaller and smaller and, um, I was guilty of the sin of pride when I was getting close to averaging 10,000 a day". [Interviewee No. 9, male, aged 60].
>
> "To do the six months, it motivated me quite a lot, and especially the chats because I was saying ah, I want to meet my 10,000 goal". [Interviewee No. 14, female, aged 51].
>
> "Well I mean I, I'm hooked on it. When I did, you know, that 14,000 steps one day, I was staggered". [Interviewee No. 17, male, aged 67].

Memory, Attention and Decision Processes

Within this domain barriers to participation and achievement of goals included HIV-related memory loss. This was a factor in the decision not to participate in the intervention. It was felt that achieving daily goals and attending appointments would be stressful given the degree of memory loss experienced:

> "I just kind of feel I've missed so many appointments, um, I'm not certain why I've missed them. There was something that was showing up on the blood test – the cholesterol – it was something to do with the liver. I can't remember – it was something that was abnormally high. They did it at the GP surgery, and I had three tests, and then they made an appointment for an ultrasound, and I got the dates all mixed up. I mean I was going, but in the end it was like I just got it all mixed up. I'm not so good at keeping appointments or making commitments to things any more". [Interviewee No. 5, male, aged 63].

Within the trial, participants with impaired memory were able to achieve goals through use of diaries and other practical tools.

The relative chaos in daily living experienced by some people living with HIV was cited as a barrier to change, in terms of the effect on attention to achieving goals and overall decision making. However, through careful attention they were able to overcome this barrier:

> "I was a bit more careful of what I was eating. I paid a bit more attention to the food in front of me than I used to do. Doing this study made me think before I ate something". [Interviewee No. 2, male, aged 64].

Environmental Context and Resources

Logistics were found to be both barriers and enablers to change. Some found the location easy to get to whereas others found the distance problematic. Work life prevented participation where time off to attend research appointments would either not be granted or would result in the participant being compelled to disclose health issues. Work pressures limited ability to adopt healthier eating behaviours and the ability to exercise. However, careful attention to this, particularly seeking support from colleagues, proved to be an enabler. Here participants felt able to disclose to colleagues and managers risk of diabetes but not HIV status.

Barriers to participation included attending too many healthcare appointments at present. It was felt that regular research appointments would add to this burden. Additionally, a feeling that too much was happening in life in general was a barrier to committing to taking part.

Healthier foods were generally perceived to be more expensive. For example among African-origin participants increasing consumption of leafy green vegetables was prohibitively expensive for those who ate imported African greens exclusively. Some African participants found cheaper UK-grown greens acceptable, as did those of Caribbean-origin. Participants talked about strategies to limit this extra expense but for most this continued to present as a barrier. Reimbursement of travel expenses was appreciated as an enabler to participation.

Weather, rain, cold and extremes of heat, and fewer hours of daylight in the winter were reported to limit the ability to exercise.

Social Influences and Group Norms

Social life both enabled and prevented change:

> "And then it comes to lunch. I have with me my creatively designed with all colours in it. Make the whole office envious of me." [Interviewee No. 15, female, aged 42].

> "It's very, very difficult to give these up especially when you go to some party. They will give you more sweets and you have to say them ok control, control, you shouldn't eat that but that won't come all of a sudden". [Interviewee No. 13, male, aged 40].

Drinking culture in pubs and clubs was challenging for those who habitually consumed higher amounts of alcohol. Eating with family was a barrier to change:

> "My son who loves, enjoys me having that fish and chips on a Friday and some of my grandchildren's food cos sometimes I eat with my grandchildren. So I had to sort of reduce eating with them. Cos their food is normally a lot fattier and all that". [Interviewee No. 4, female, aged 55].

Societal pressure to lose weight and attain a normal BMI was evident as a motivator.

> "I looked at myself side on in the mirror and I thought would you sleep with you and I thought no I wouldn't". [Interviewee No. 9, male, aged 60].

> "It was good and it has made me lose weight and made me look even, yeah, it makes me look even younger, let me say". [Interviewee No. 8, female, aged 48].

Among gay men who self-identified as bears, lack of partner support, positive acceptance of overweight and the confidence gained from having a higher BMI and being attractive were barriers to change, limiting motivation to lose weight:

> "My partner likes me being a bigger guy. A few months in when I was struggling and I mentioned, he said, well, you know, I told you, I told you not to do this and you ignored me". [Interviewee No. 23, aged 41].

Emotions, Anxiety and Fears

Fear of developing diabetes was a powerful motivator to change behaviour. Other factors within this domain were HIV-specific. Fear that deliberate weight loss would disclose HIV status was a barrier to achieving goals. Concerns about confidentiality and disclosure of HIV status, and trial participation being a constant unwelcome reminder of living with HIV were barriers to consenting to participate.

Behavioural Regulation and Self-monitoring

For those with an external health locus of control the pedometer was cited as a useful tool to self-monitor physical activity levels, particularly as a way to gradually increase towards or maintain goals. In terms of healthier eating, planning, eating in moderation, and a stepwise approach were all enablers to change:

> "So it was just finding means of, as opposed to having excuses, I started thinking OK, here's a challenge but how can I make it work? So I did not use excuses. I found solutions for the challenges and to me it was a vegetable market. So Sunday take my little trolley instead of getting into a car and walk to the market and pick up all sorts of different fruit and vegetables for whatever's planned on my menu for the week. So I'm not wasting money going into the express supermarkets. I've got everything at home. Buying things randomly you end up spending a whole lot of money". [Interviewee No. 15, female, aged 42].

> "But if you eat smaller proportions, portions, model yourself on our dear Queen. If she can stay thin, so can we". [Interviewee No. 11, male, aged 63].

> "What I do now is I don't eat them as often. Steak and kidney pudding with mash. Then I won't have that for another fortnight". [Interviewee No. 3, male, aged 44].

Synthesis of Enablers and Barriers:

General Enablers

Having positive beliefs, self-confidence and an optimistic approach were key to successfully achieving goals. A belief that lifestyle change could reduce disease risk and a desire to prevent diabetes had a positive impact. Societal pressure to lose weight was evident as a motivator to change. Improved knowledge and skills, overcoming isolation, commitment to succeed and a desire to tackle obesity were strong enablers. Planning, a stepwise approach and use of a pedometer as a tool to monitor building towards and achievement of goals were enablers. Ease of travel to consultations and reimbursement of travel expenses were also enablers to participation.

General Barriers

Cultural and societal barriers included the societal valorisation of obesity in African cultures and among gay men identifying as bears. Lack of support from partners, friends and the wider community was problematic. Conflicting advice regarding healthier options and behaviours was cited as a barrier. Healthier foods were perceived to be more expensive and, for some, unfamiliar. Lack of commitment and willpower were significant barriers to change. An excess of external pressures at work or home, bad weather and fewer daylight hours in the winter months and pressures in social life all limited ability to change behaviours.

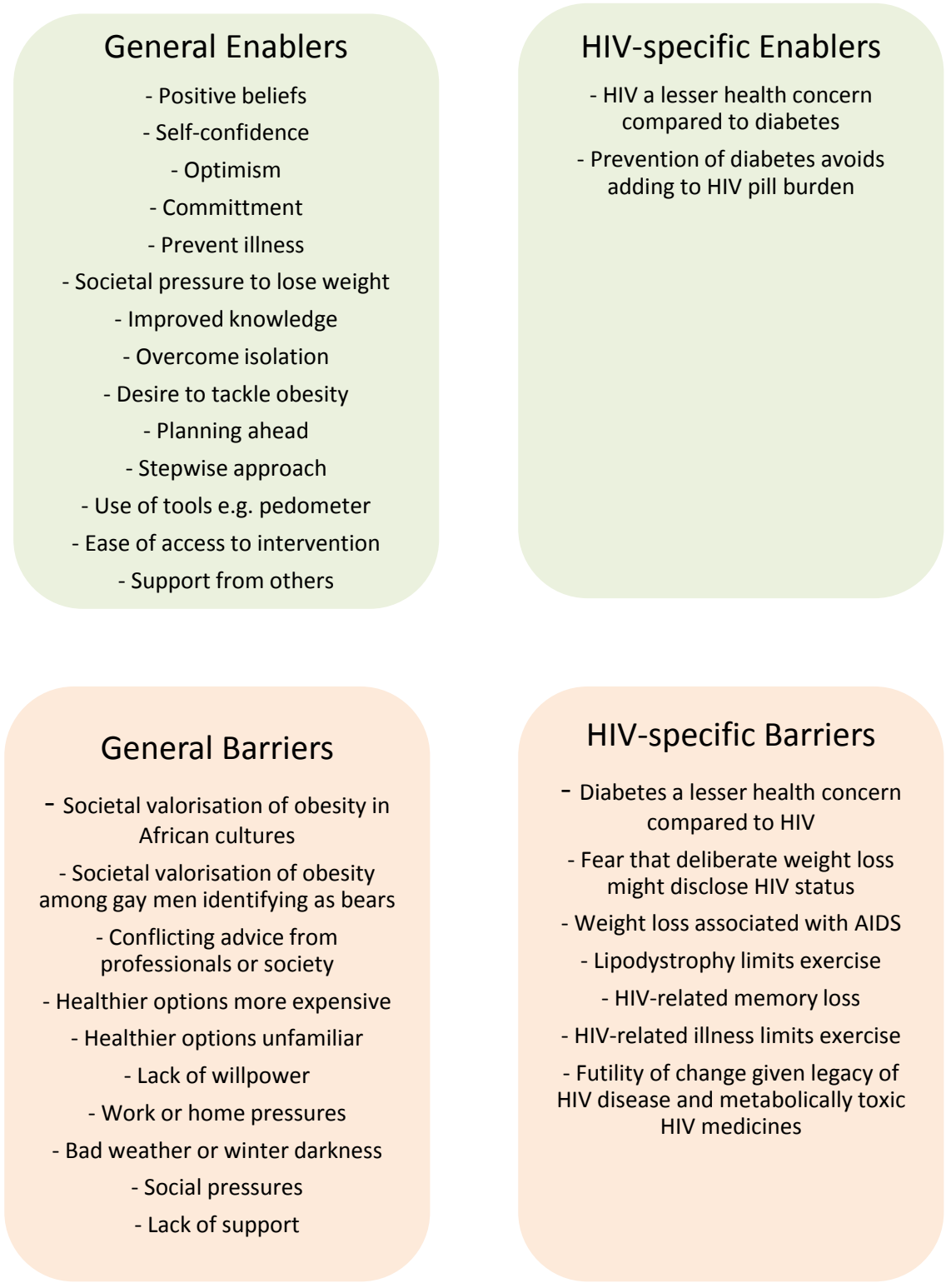
HIV-specific Enablers

Those who felt that HIV was largely controlled and a lesser health burden compared to diabetes were motivated to change behaviours. Avoiding adding to pill burden was an enabler.

HIV-specific Barriers

Those who felt diabetes was a lesser health concern compared to HIV were less motivated to change behaviours. Across ethnicities but particularly among the African community, thinness may be associated with AIDS and this fear of disclosure of HIV status or association with memories of AIDS acted as a barrier to achieving weight loss goals. Lipodystrophy, HIV-related memory loss, a lower BMI secondary to HIV-related illness and HIV-related illnesses themselves all limited ability to change behaviour. Lifestyle change was considered futile given the legacy of HIV and associated medicines.

Figure 27: Enablers and Barriers to Lifestyle Change



3.4.10 The Acceptability of the Intervention

Interviewees found methods of recruitment to the study acceptable. Detailed description of study procedures, time commitment and explanation of potential benefit and risk was appreciated. Opinion was divided regarding patient information. The patient information leaflet was overly-long and complex for some, whereas others reported reading it through from start to finish and finding it helpful. Food diaries were problematic for some to complete, whereas others reported finding them helpful as a tool to aid dietary change:

> "I'm not sure if the food diary was mentioned to me at the start. I found that a bloody nuisance. I'd forget to write down what I'd had, and I'd have to scribble down on bits of envelopes. I then had to transfer and keep checking the book. I found it just a bit… a bit too much". [Interviewee No. 2, male, aged 64].

> "I won't say I'm OCD but once I get going, I like to note everything down. The food diary was quite interesting. I find it quite interesting to see what, and to note what one does eat and how often and what, that sort of thing. It was quite an interesting piece of work really". [Interviewee No. 11, male, aged 63].

Typical duration for the visit on Day 1 was four hours. The Frequently Sampled Liquid Meal Tolerance Test (FSLMTT) procedure itself was 3 hours 15 minutes, assuming initial cannulation was successful. In total 90ml blood was taken via the cannula. Interviewees again offered a spectrum of views, from no concerns or issues to the procedure through a middle ground of dislike of phlebotomy but resignation to the necessity of the test, to an outspoken intolerance of the procedure:

> "I must admit, it didn't bother me. I mean, they've taken so much blood over the years, it's no big deal". [Interviewee No. 12, male, aged 63].

> "A nightmare… This one was maybe three hours. So that was the part of it. It was the fact that the needle was in my arm all the time and the blood being pulling. I would wish that it could have done in a shorter time". [Interviewee No. 10, male, aged 44].

Questionnaires were largely acceptable. They were reported as being fun and a distraction from the 3-hour blood test although some interviewees found questions regarding sexual functioning and financial position intrusive.

Regarding intervention design participants found the frequency of the monthly appointments acceptable, although suggestions were made for a more flexible approach with fewer or more

appointments. Interviewees who declined to take part in the intervention attributed in part this decision to being unwilling or unable to attend monthly appointments:

> "Well in my case just having to drag myself up there regularly during the rush hour when I've fasted because I find fasting very very difficult because I don't have the reserves of fat, so when I fast I'm really really hungry and I feel weak". [Interviewee No. 1, male. Aged 71].

Food samples provided on Day 30 were found useful to explore reduced fat, reduced salt or wholegrain alternatives. Interviewees valued the opportunity to try foods outside their usual consumption. Some anxieties were expressed regarding receipt of free samples and the cost involved to the funder of the study. Use of the Clinical Research Facility for appointments and joint support from myself and the research nurse, described by the participants as collaboration, was particularly welcomed:

> "Very relaxed. Very nice environment. Felt quite at home". [Interviewee No. 2, male, aged 67].

> "It was seeing a place like this which was very quiet in comparison to the rest of the world, the surrounding hospital". [Participant No 11, male, aged 63].

> "We were chatting and all, all of us were participating. I feel a part of what was going on". [Interviewee No 10, male, aged 44].

Behaviour change techniques were largely acceptable, with interviewees appreciating the stepwise approach to achieving goals. However, a more directive and educational model was also suggested:

> "I think there is a degree where you would need some kind of intervention. Not so much people coming back all the time to be measured and weighed but you know like a trainer that you work out with three times a week or something that forces the average person to do this who just isn't naturally inclined to do it. I think that would be great. You're talking about gyms or trainers, that's really expensive. If we're talking about skyping with a dietary counsellor, I think that would be cost-effective, probably". [Interviewee No. 22, male, aged 46].

Support from myself was appreciated, as were motivational and reminder texts and emails. Interviewees suggested additional support from exercise instructors, online resources and group sessions:

> "So it's actually touched in so many different parts of my life you know, that, which I could have never done on my own, without this and without your support". [Interviewee No. 15, female, aged 42].

> "Maybe have other things tied into it, like a gym group, or an exercise group, or having contacts that people can then contact themselves. Because if they approach an organisation themselves, that is self-motivating". [Interviewee No. 3, male, aged 44].

3.4.11 Attitudes to Research Participation

The interviewees' motivation for research participation was for reasons of altruism and directly described personal benefit. Rather than one or the other most participants mentioned a combination of the two motivators for participating in this and other research studies:

> "What I'm doing might help people further down the line. I'm on my way out, so, for the younger people that are coming in with these problems, what I'm doing may help them". [Interviewee No. 2, male, aged 64].

> "If I think the research will benefit me and it's not going to be a huge burden, I'll consider it". [Interviewee No. 22, male, aged 46].

> "I think a lot of people think it might be no benefit to them, but I think all increased knowledge is beneficial to me". [Interviewee No. 19, male, aged 57].

Practical barriers to research participation were mentioned, including logistic issues such as difficulty taking time off work and financial issues despite being able to reclaim travel costs. Participation in commercial product development studies was compared with medical research, with the suggestion made that financial incentives might encourage research involvement. Interviewees suggested offering evening or weekend research appointments. Confusing or over-technical participant information was a barrier to participation, with interviewees stating that they were unlikely to read large documents. Participants also mentioned HIV-related motivators and barriers to research participation. Motivators included

the desire to find out more about the effects of HIV and HIV medicines and the potential to find a cure for HIV. The frequency of extra support and monitoring was described as reassuring by participants who had lived with HIV for a longer duration and previously experienced illness and side effects. Barriers included being reminded about HIV-related illness:

> "I think Mae West once said it's better to be looked over than overlooked [laughs]. And I think it's that sort of situation really with research, you know". [Interviewee No. 17, male, aged 67].

> "The other problem I think is, particularly with something like HIV and diabetes, is that if you're doing the research it constantly reminds you that you've got something wrong with you and you might want to ignore it. That's a sort of psychological thing that if you're taking part in the research, that means you're ill and you can't ignore it". [Interviewee No. 21, male, aged 59].

Participants discussed avoidance of participation in trials of HIV medicines. Experiences from previous trials had been unfortunate for some and others were wary of the level of invasiveness of the study:

> "I don't like those medicine studies because I don't know what they are trying on me". [Interviewee No. 8, female, aged 48].

> "When we talked I found out it's nothing to do with anything being put in my body. It's just taking blood out and testing on it and me making changes here and there. I was happy doing that because it did not involve me consuming anything that's artificial into my body". [Interviewee No. 15, female, aged 42].

Experience by a sub-group of participation in previous research studies was mixed. Participants described taking part in trials of new HIV medicines and how they felt this had kept them alive, whereas others described more negative experiences with unfortunate side-effects, attributing this historic exposure to current poor health:

> "I was asked by [Doctor's name] to do the hepatitis C trial. God, I wish I'd said no. It was the worst time of my entire life. Diarrhoea, vomiting, everything, you name it. I suffer for the year or 53 weeks or something, I can't remember how long. But it's almost a year. Is the worst time of my life". [Interviewee No. 10, male, aged 44].

Research participation was described as fun by some. The social aspect of contact with health professionals was valued. Others wanted to participate but felt disenfranchised by being over the eligible age limit for most studies or felt they had been used:

> "I felt a bit like I was being treated well when I was of interest and then I kind of got dumped when I wasn't eligible, and I think there is something there about making sure people don't feel like they're being used". [Interviewee No. 23, male, aged 41].

Confidentiality was paramount for participants. Reassurance of non-disclosure of status, use of identity codes rather than names when recording study data, sensitivity to methods of contact and confidentiality when disseminating findings were all mentioned as facilitators to research participation:

> "I need to keep it to myself. I don't want to tell for everybody. It's, [HIV] it's confidential". [Interviewee No. 20, male, aged 50].

> "I remember my worry was, the first question I asked you is I don't want my status of HIV to come open, and you say no, everything is confidential. So after you've told me, I was like comfortable with everything". [Interviewee No. 7, female, aged 49].

> "And then also even though I knew it's confidential, at the back of your mind you're kind of like thinking who else is going to be looking at this information. I know you sort of explained to me that it's all confidential and we number each person by number as opposed to a name. But still at the back of my mind I was kind of thinking to myself oh, it's just one of those tricks those people use". [Interviewee No. 15, female, aged 42].

Fear of disclosure of HIV status prevented participation in this study:

> "I wouldn't have felt I'd been able to do it because I might have to explain to people at work what I was doing and I wouldn't necessarily want to do that". [Interviewee No. 18, male, aged 45].

Interviewees suggested that to encourage others to take part in research, clear explanation of benefit and risk should be made. Dissemination of results to participants was felt to be key. To improve recruitment to studies, interviewees suggested that patients should be approached initially by health care professionals other than physicians.

3.4.12 Overarching Typologies

Typologies were developed to apply a range of phenomena to categories of participant. For this exercise those who were withdrawn from the study were not included as their response to the intervention is unknown. The remaining 16 participants included in the typology were comprised of 4 who declined to take part in the intervention, 4 who completed the intervention achieving 2 or fewer goals and therefore classified as poor achievers, and 8 who completed the intervention performing moderately or well by achieving 3 or more goals. The typology constructed has multiple linkages where more than one position from each dimension is found in certain cells (Table 3.36).

Table 3.36: Analysis of Interviews: Multiple Linkage Typologies

	Declined Participation	Achieved Intervention Goals Poorly	Achieved Intervention Goals Moderately / Well
Health Locus of Control	***External:*** HIV medicines blamed for obesity or increased diabetes risk	***External:*** Lack of success blamed on HIV medicines, HIV-related illness, or social pressures	***Internal:*** Recognised diabetes risk could be mitigated through change in own behaviour
Identity	Not applicable	Weight loss was associated with loss of identity	Weight loss not associated with loss of identity ***OR*** Content with change in identity associated with weight loss
HIV and Diabetes	HIV worse than diabetes	HIV worse than diabetes ***OR*** Same as each other but *unmanageable*	Diabetes worse than HIV ***OR*** Same as each other but *manageable*
Support	Somewhat or completely isolated	Limited support or opposition	High level of support
Priorities	Trivialisation of diabetes risk and prioritisation of other issues	Prioritisation of keeping HIV secret	Participants prioritised overcoming barriers through self-efficacy or with support

Those Who Declined to Take Part in the Intervention:

Using this typology those participants who declined to take part in the intervention were characterised by a sense of loss of control over their health. HIV medicines were blamed for their increased diabetes risk and weight issues, either obesity or underweight. They expressed a sense of injustice at developing increased risk of diabetes:

> "I think most diabetics it's their own fault, so I'm very annoyed if you think I might get it, because I think I'm a very sensible eater, and my lifestyle is pretty good". [Interviewee No 1, male, aged 71].

> "Well I knew that as soon as I went on a protease inhibitor based regime that it [diabetes risk] would go up. [Interviewee No. 22, male, aged 46].

HIV was felt to be a more serious condition than type 2 diabetes. Diabetes as a condition was trivialised or deprioritised. Other issues were given priority, including relatively minor health concerns. Those who declined to take part were also either profoundly self-isolating from society or tended to self-isolate with interactions limited to partners or online.

Those Who Achieved Intervention Goals Poorly

Those participants who achieved 2 or fewer of the 10 intervention goals were also characterised by a sense of loss of control over their health. HIV medicines were blamed for their underachievement in the intervention along with HIV-related illness and social issues such as pressure of work. Deliberate loss of weight, an intervention goal, was associated with loss of identity. Here, being overweight was self-identified as an attribute within the bear or African communities. They had expressed relative contentment with body image before embarking in the intervention:

> "Well I'm not vain about that [*body shape before intervention*]. No it doesn't bother me. For 67, not too bad". [Interviewee No. 17, male, aged 67].

HIV was believed to be either a more serious or equal health concern compared to type 2 diabetes. A lack of support or indeed opposition to achieving intervention goals characterised this group. Additionally they sought less support from health professionals throughout the intervention. In terms of barriers to change, this group was characterised by a either a fear of disclosure of HIV status through deliberate weight loss or, in the absence of this, limited self-efficacy.

Those Who Achieved Intervention Goals Moderately or Well

Those participants who achieved 3 or more of the 10 intervention goals were characterised by a sense of control over their health. They recognised the possibility of mitigating diabetes risk through changing their eating and exercise habits, and found ways to overcome barriers to

change. Deliberate weight loss was not associated with loss of identity or for those who recognised this was a possibility, they came to terms with this:

> "I don't need the approval of other people to the extent that I would put my health at risk to maintain an unhealthy shape". [Interviewee No. 23, male, aged 41].

Diabetes was felt to be either a more serious health concern than HIV or of equal concern to HIV. However, both were considered to be manageable. There was a high level of support from others, or a high level of support sought from health professionals from those who were relatively isolated.

Implications of typologies are discussed in Section 4.4, along with a general discussion of findings from the in-depth interviews.

4 DISCUSSION

> *'the effectiveness of the pilot intervention demonstrates the potential to reduce risk for type 2 diabetes in HIV'*

4.1 Principal Findings

In this thesis I have presented, to the best of my knowledge from literature and trial registry reviews, the first cross-sectional study describing in detail the phenotype of dysglycaemia in people living with HIV in the UK, a diet and exercise intervention specifically designed to reduce insulin resistance in people living with both HIV and prediabetes and an in-depth investigation of attitudes to diet and exercise change in people living with HIV. In this section I have presented a summary of key findings, and subsequently discuss each of these in turn.

In this ethnically diverse antiretroviral-experienced London-based HIV cohort, type 2 diabetes was highly prevalent. In 2005, 6.8% had been diagnosed with T2D and by 2015 this figure was 15.1%. This compares with a London-wide prevalence of T2D of 4.5% in 2005 rising to 6.0% in 2015 (Diabetes UK, 2015). Almost two-thirds of the 2015 HIV cohort had central obesity, four out of ten had hypertension and three out of ten metabolic syndrome.

Logistic regression analysis suggested that the conventional risk factors hepatic steatosis (OR 7.28) and hypertension (OR 2.58) made a greater contribution to association with risk of dysglycaemia than other factors. HIV-specific factors also contributed to dysglycaemia risk, principally weight gain in the first year following initiation of anti-HIV therapy and duration of HIV infection. Modifiable factors made a significantly greater contribution to association with risk of dysglycaemia than fixed factors (probability of predicting dysglycaemia 0.838 and 0.752 respectively, p=0.029 for difference in proportions), suggesting that lifestyle change mitigating hepatic steatosis and hypertension through weight loss has an important role in diabetes prevention among people living with HIV.

The 28 participants with prediabetes and HIV who completed the 6-month diet and physical activity intervention experienced a mean reduction in weight of 4.1 kg (4.7%) and waist 6.6cm (6.2%). Following the lifestyle intervention these clinically significant outcomes were

accompanied by reductions in fasting levels and 3-hour incremental area under the curve for insulin and glucose, the HOMA insulin resistance index and the glucose disposal rate calculated using the Mari method. Significant reductions were made in other secondary outcomes including percentage body fat, triglyceride levels and blood pressure, and significant increases in HDL and life satisfaction.

The intervention was largely acceptable to participants. Confidentiality issues and fear of disclosure of HIV status were key themes emerging from interviews. There was a diversity of achievement of intervention goals within the 28 intervention participants; the qualitative research study identified enablers and barriers to achievement of diet and exercise change.

Those who declined participation or achieved fewer intervention goals blamed diabetes risk on HIV medicines, and inability to adopt healthier lifestyle behaviours on external factors such as bad weather or financial barriers. They were characterised by an external health locus of control, and prioritised factors other than diabetes risk-related health. Those who achieved more goals expressed an internal health locus of control. They considered prediabetes treatable and type 2 diabetes avoidable. They found ways to prioritise overcoming barriers, either through internal health locus of control or through seeking support.

The most prominent enablers to lifestyle change were a desire to avoid adding to pill or disease burden and a strong support network. The most significant barriers were fear of deliberate weight loss leading to loss of cultural identity and disclosure of HIV status.

4.2 Phenotype of Dysglycaemia in HIV

4.2.1 Discussion of Results

This study aimed to describe the phenotype of prediabetes and type 2 diabetes in people living with HIV in the UK and how this has changed over time. In summary, approximately 1 in 3 of this ethnically diverse, London-based cohort had prediabetes or T2D. Comparing data with that collected 10 years earlier T2D prevalence was observed to have more than doubled from 6.8% to 15.1%. A range of HIV-specific and conventional risk factors appears to be associated with this disproportionate increase in T2D, with the modifiable risk factors hepatic steatosis and hypertension contributing the greatest odds ratios for association with dysglycaemia.

Cohort Characteristics

The 2015 cohort reflected the diversity of people living with HIV in the UK, with 2014 figures for the UK previously described on page 21. The use of ARVs was widespread in this cohort, exceeding the WHO target of 90% of PLWH receiving therapy. The prevalence of undernutrition was very low at 2.4%, reflecting the benefits of successful ARV treatment, prior to which rates of undernutrition were 10 times as high, as described in Table 1.4. Conversely, the rates of overweight and obesity were 58.0% in 2015 compared to 47.9% ten years earlier, now comparable to the 58.4% rate in the general London population (Public Health England, 2015b). The cohort experienced considerable metabolic burden, with high rates of hypertension, hyperlipidaemia requiring statin therapy and central obesity. These contributing factors resulted in a metabolic syndrome prevalence of almost one third. This metabolic burden is greater than that published by investigators from two large studies of people living with HIV, one from the USA and one multinational, where the prevalence of overweight and obesity was 25% and 43% respectively (Willig et al., 2015, Yuh et al., 2015). This observed difference may be due to the diversity of ethnicity in the UK cohort where non-Whites comprise the majority, compared to the USA and multinational cohorts where White participants comprise the majority. Hypertension and obesity are more common in African and Caribbean origin people living in the UK (Public Health England, 2015b). This appears to be polarised among participants in this HIV study, where, for example, 16.6% of White women were overweight or obese, compared to 84.3% of Black African women.

Health habits of this HIV cohort differ from those of the general London population. Although smoking rates in this cohort were significantly lower in 2015 compared to 2005, at 21.0% they remain higher than the overall London rates of 17% (Public Health England, 2015b). Almost one half of participants are sedentary, compared to a London-wide rate of one quarter (Public Health England, 2015b). However, these comparisons should be treated with caution as sampling and data collection methods were different. The reduction in rates of smoking is significant among a population at higher risk for CVD and cancer, as described earlier in Table 1.3. However, encouraging physical activity should be a key message for self-care.

Prevalence of Dysglycaemia

The burden of prediabetes in this cohort appears to have remained steady with an 18.1% prevalence in 2005 compared to 17.2% in 2015, whereas T2D appears to be highly prevalent, increasing from 6.8% to 15.1%. For comparative illustration the prevalence of T2D in the

general London population is around 6%. However, the median age of Londoners is 39 years, 10 years younger than this HIV cohort. Diabetes prevalence data from the general England and Wales population has been stratified by 10-year age band (Diabetes UK, 2015). The prevalence of T2D among those aged 40-49 and 50-59 in England and Wales is 10.7% and 18.9% respectively. This compares to a prevalence from this HIV cohort of 13.9% and 19.2% respectively. I have presented these comparisons for illustrative purposes only, as without recruiting HIV negative participants and matching them to HIV positive participants by age, gender, ethnicity, and BMI, for example, the value of extrapolating population comparisons is extremely limited.

There is little published information about changes in prevalence of T2D in PLWH elsewhere, but a change in incidence of T2D has been observed in an ethnically diverse HIV cohort in France (Capeau et al., 2012). Investigators reported an incidence of T2D of 2.7 per 1000 person years of follow up in 2005, rising to 5.0 in 2009. This rise in incidence was associated with age and obesity, and historic exposure to ARVs linked with metabolic toxicities. A study of a Danish population showed no increased risk for T2D in HIV. However, this study was confined to White participants, the cohort was relatively young, and had lower levels of obesity compared to the cohort presented in this thesis (Rasmussen et al., 2012).

The very high prevalence of T2D in 2015 in the cohort presented in this thesis exceeded the upper end of a range in HIV patients that in a review (Hadigan and Kattakuzhy, 2014) has been described as 2.6% (Rasmussen et al., 2012) to 14% (Brown et al., 2005). This may in part reflect collection of data from this cohort as recently as May 2015 and may be a portent of changes occurring more widely. This may also reflect socioeconomic challenges faced by a high proportion of participants. There was a strong correlation between employment status and dysglycaemia. The majority of those with T2D were unemployed. This resonates with a French study which found unemployment conferred a five times higher risk for developing T2D in PLWH (Dray-Spira et al., 2012).

It is not clear how rates of prediabetes and T2D in this cohort may change over the next 10 years. Without prevention strategies, assuming a continuation of T2D incidence observed between 2005 and 2015, and assuming continued HIV diagnosis rates (Public Health England, 2015a), the prevalence of T2D in this HIV cohort could reach 25% by 2025. Extrapolated to the wider UK HIV cohort, this would equate to 15,000 new diagnoses of T2D by 2025. It could be argued that a reduction in the T2D incidence rate may be observed over the next 10 years,

reflecting the widespread cessation of use of those ARVs associated with increasing diabetes risk. However, the regression analysis presented in Section 3.2.5 suggested that modifiable factors associated with obesity (hepatic steatosis and hypertension) provide the greater contribution to diabetes risk in this population. Obesity rates increased from 47.9% in 2005 to 58.0% in 2015. If this rate of increase continues, by 2025 up to 70% of this HIV cohort may be overweight or obese, and this may exacerbate the T2D incidence rate. There appears to be a clear imperative to treat and prevent both obesity and T2D risk in people living with HIV.

Factors Associated with Dysglycaemia

The duration of HIV infection, ARV treatment and particularly the use of metabolically toxic ARVs, weight gain following initiation of ARVs and the presence of lipodystrophy were all significantly associated with an increased risk of dysglycaemia. These findings agree with studies from a range of cohorts (Samaras, 2012) (Achhra et al., 2015). However, in contrast to these studies there was no correlation between CD4 nadir. This could be related to different historic HIV treatment guidelines in the UK where ARVs were largely initiated before the CD4 count could decline below 350 (Asboe et al., 2012).

Age was strongly associated with dysglycaemia: all participants with prediabetes or T2D were aged 39 or over. Central obesity, BMI, hypertension, HDL, triglycerides, hepatic steatosis, corticosteroid exposure, physical activity and statin use were all associated with dysglycaemia. Again, these findings resonate with other studies of HIV cohorts. However, there was no significant correlation between either ethnicity or gender and dysglycaemia in either 2005 or 2015. Although the lack of correlation between ethnicity and diabetes risk is consistent with other investigations of European HIV cohorts (Capeau et al., 2012), there is a direct contrast with European-wide systematic review findings where, for example, controlling for other factors those of sub-Saharan origin were found to have an odds ratio of 2.6 for development of T2D compared to the host populations studied (Meeks et al., 2016). The lack of correlation in HIV may be due to the unique diversity of the London-based cohort studied, with participants born in over 60 countries. Alternatively confounders including age, polarised gender and ethnic differences, or contribution to diabetes risk from HIV-related factors may have increased comparative risk among Whites.

T2D in this HIV cohort was significantly associated with lower socioeconomic status and unemployment. This resonates with findings from the UK as a whole, where in terms of risk for development of T2D lower wealth was found to confer an odds ratio of 1.56 and 2.08 for men

and women respectively (Tanaka et al., 2012). Lower socioeconomic status despite high levels of further education reflect the legacy of chronic illness in this HIV cohort, where onset of HIV infection occurred at a relatively young age leading to many experiencing long periods of poor health, an uncertain future and unemployment (Ibrahim et al., 2008). Although three-quarters of the cohort had completed further education, a high attainment level, almost one-third were unemployed and one-fifth reported to be in current financial crisis. This high level of unemployment and its association with diabetes risk warrants concern. A holistic approach to healthcare for PLWH might include onward referral for support for those who are unemployed or in financial crisis (Pelham-Burn et al., 2016).

Modifiable factors contributed significantly more to risk of dysglycaemia than fixed factors, including age. Hepatic steatosis and hypertension contributed the greater risk for dysglycaemia. These findings add weight to the argument for early diagnosis of risk factors, screening for dysglycaemia and diet and exercise interventions implemented in HIV clinics, aimed at preventing T2D rather than providing diabetes treatments that may be suboptimal (Han et al., 2012). Findings from this study suggests that lifestyle change mitigating hepatic steatosis and hypertension through weight loss may have an important role in diabetes prevention among people living with HIV.

Dietary Analysis

The diet diary completion and return rate of 58.6% was relatively high compared with other studies (Cantwell et al., 2006). Taken as a sub-set, diary completers were statistically similar to the complete cohort in all factors measured in the sensitivity analysis other than age ($p=0.019$). However, the mean age difference of 2 years should not be considered clinically significant.

The adapted Goldberg method as a marker of underreporting (Livingstone and Black, 2003) identified 46.5% of participants likely to have underreported intake, and the NHS Nurses study method (Mendez et al., 2011) suggested that 3.5% of participants reported an unfeasible intake. This relatively high rate of underreporting using the Goldberg method compares to high rates observed in other studies, for example 34% in a recently published UK–based investigation (Pettitt et al., 2016) and 25.1% in a US study (Murakami and Livingstone, 2015), and may in part be due to an overestimation of energy expenditure, perhaps likely given the high levels of sedentary behaviour in this cohort. However, under-reporters had a significantly higher BMI, a correlation reported widely in other studies (Poslusna et al., 2009). Investigators

have proposed excluding those participants with unfeasibly low energy intakes from dietary cohort analyses to reduce inaccuracy of analysis (Smith et al., 1994). However, investigators conducting a recent analysis of the NHS Nurses study (Rhee et al., 2015) found that excluding under-reporters using the Goldberg method resulted in selection bias. They repeated the analysis using the simple unfeasible intake method, and found dietary correlations were supported by biomarker analysis. They concluded that there was no benefit from using complex estimation equations for assessment of misreporting dietary intake.

Further investigation of underreporting or unfeasible intakes should be taken in future analyses of data produced from this study. Exclusion of 46.5% of participants suggested by the Goldberg method might result in selection bias given the associations between BMI and underreporting, and between BMI and ethnicity, prediabetes and T2D.

Future studies should consider use of new technologies to minimise underreporting and observer bias. Micro-cameras or use of in-app photography has been shown to improve accuracy of analysis of dietary intake (Pettitt et al., 2016).

Disease Risk Modelling

Current NICE guidelines suggest those with a 10-year CVD risk of 10% or more should be prescribed statins (NICE, 2014b). Prediction of 10-year CVD risk was performed using four tools, with between 19% and 39% of participants scoring a 10% or higher 10-year risk depending on prediction equation used. Previous studies investigating the use of CVD prediction equations in PLWH have demonstrated that the Framingham tool under-predicted risk for myocardial infarction and other CVD outcomes in women, in former smokers and in those with T2D, but over-predicted risk in never smokers (Friis-Moller et al., 2010). Analysis of data from this study suggests that in terms of identifying those at risk the QRisk2 tool recommended for use in the general UK population (NICE, 2014b, Hippisley-Cox et al., 2008) is comparable to the HIV-specific D:A:D prediction tool (Friis-Moller et al., 2010). For simplicity the QRisk2 tool may be used for estimating CVD risk in HIV patients pending further development of HIV-specific tools.

Three tools for predicting prediabetes and T2D were examined. The FINDRISC tool (Lindstrom, 2003) appears to confer a small improvement in detection of both prediabetes and T2D over the UK-based QDiabetes tool (Hippisley-Cox et al., 2009) and the HIV-specific D:A:D tool (Petoumenos et al., 2012).

Further examination of disease risk estimation should work towards simplification of screening and assessment. Development of a strategic approach for estimating chronic comorbid disease risk in PLWH has been called for in order to ease burden in the clinical setting (Peters et al., 2013a). Development of a single simplified tool may be possible through further analysis of data from this study.

4.2.2 Discussion of Study Design and Procedures

Strengths of Design and Procedures

The study design had three key strengths: purposive stratified random sampling to represent the diversity of the 2015 cohort; characterisation of participants by glycaemia measured in a carefully assessed fasting state in 2005 and 2015; and data collection within the broadly similar cohort of patients in 2005 and 2015 allowing a comparison over time.

The purposive sampling method combined stratification by key factors associated with dysglycaemia to ensure the sample represented the cohort. Goals to recruit a sample representative by 10-year age band, gender and ethnicity were achieved, but I was unable to recruit any participants aged 18-22. Additionally, no participants were recruited who had acquired HIV through vertical transmission, although this was not stipulated as a recruitment goal. To minimise recruitment bias, every third patient on clinic lists was screened. Clearly there was no control over which patients consented or declined to participate.

As reported elsewhere (Loutfy et al., 2014), in this study recruitment of women participants was challenging, with female quotas taking six weeks longer to meet than male quotas. Towards the end of this period I sent emails to health professional colleagues in the outpatient clinics raising awareness of the shortfall in recruiting women participants of Caribbean origin. This may have resulted in colleagues applying persuasion to potential participants to come forward. However, ethical procedures were followed at all times regarding gaining written consent to participate.

It could be argued that the stratified sampling design is open to volunteer bias. For example, participants responding to advertising might be first to fill quotas as opposed to those randomly chosen from outpatient clinic lists. Those coming forward in response to advertising might have a vested interest (Crosbie et al., 2008), for example be aware of having issues with

dysglycaemia, or have a family history of type 2 diabetes. They might also have achieved higher levels of education and be more open to research participation, a form of volunteer bias observed in other studies (Martinson et al., 2010). In fact, few participants were recruited in response to advertising, contributing 1% of the final total. However, three quarters of participants had completed further education, compared to 40% in the UK, and reported rates of up to 60% of job-seekers in London (The Office for National Statistics, 2013). Further work is needed to ascertain whether the high level of educational attainment observed in study participants is representative of the wider cohort.

Limitations of Design and Procedures

Limitations included a difference of sampling methods between the two time points. The 2005 cohort was selected at random and represented a 40% sample of the cohort. By 2015 the numbers of patients attending HIV outpatients had increased significantly. Taken together with time constraints, recruiting a 40% sample in 2015 was unfeasible. When comparing changes between 2005 and 2015 an assumption must be made that both samples are statistically representative of their respective cohorts as this cannot be proven.

Medical records predating 1996 were rarely available, with data collection instead relying on participant recollection; 18.6% of participants were diagnosed with HIV prior to 1996, and 8.9% of participants initiated ARVs prior to 1996. Variables such as date of diagnosis of HIV, date of initiation of first ARVs, and weight change following initiation of HAART potentially took place up to 25 years prior to data collection, and recollection may not have been wholly accurate. However, investigators have demonstrated that recall of past weight over 10-year age bands can be relatively accurate (Kyulo et al., 2012). They reported that recall of weight from 26 years previously was underestimated by a mean of 0.67 kg, becoming more inaccurate as participant age increased over 70 years. There was the potential for misreporting of smoking status, physical activity and consumption of fruits and vegetables secondary to a perceived need to please the researcher.

Hepatic steatosis rates may have been overestimated in those with dysglycaemia due to selective clinical screening in those perceived to be at risk of hepatic fibrosis. Conversely, although a sizeable minority of participants had been screened, given the association of overweight with hepatic steatosis (Price et al., 2014), and the relatively high mean BMI of the cohort, cases of steatosis may have been missed. It could be argued that direct assessment of hepatic steatosis by Fibroscan in all participants should have been measured in the cross-

sectional study, and additionally pre- and post-intervention. The test is non-invasive, can be performed in 15 minutes and requires limited training (Sasso et al., 2016). However, due to financial and logistical constraints and recent development of the technique it was not possible to include this technique in the studies presented in this thesis. I would recommend future studies include assessment of hepatic steatosis using either Fibroscan or computed tomography scanning techniques, although the latter method involves exposure to radiation (Sasso et al., 2016).

The glycaemic status of participants was defined by a single measure of fasting glucose. It could be argued that given the inherent variability of fasting glucose measures, a repeat measure to confirm glycaemic state would have been preferred. In a meta-analysis of studies where the reproducibility of glucose measures was investigated, statistical analysis of repeated measures indicated poor to fair agreement for IGT and moderate agreement for IFG (Balion et al., 2007). The average reproducibility was lowest (49%) for prediabetes compared to diabetes (73%) or normoglycaemia (93%). Given the lower reproducibility with prediabetes, future investigations should consider the use of repeated measures and protocol decisions where disagreement occurs.

Choice of Methodologies

Data collection procedures were acceptable, with virtually no missing data resulting and with clinical assessment visits lasting less than 60 minutes, there was minimal burden for participants. Scales used to measure socioeconomic status were acceptable as no direct questions were asked regarding income. Studies have found that non-response rates for questions regarding income are higher than questions generally regarded as highly sensitive including number of sexual partners or date of first menses (Tourangeau and Yan, 2007). The MacArthur scales used additionally to the National Socioeconomic Classification (NSEC) proved useful. The MacArthur UK scale asked participants to place themselves on a Likert scale comparing themselves against others in the UK in terms of employment, financial situation, education level and influence (Adler et al., 2000). Scoring on this scale agreed with the NSEC, since both indicated participants with T2D to be socially disadvantaged compared to others. However, the MacArthur Community scale scores were statistically similar. This scale asked participants to place themselves on a Likert scale comparing themselves against others within their own self-defined community. The implication here is that support or influence at the community level has a beneficial effect on health. This has been reported in studies

investigating PLWH outside of Europe (Basavaraj et al., 2010) and warrants a fuller investigation in people living with HIV in the UK.

The logistic regression models stratified factors associated with dysglycaemia according to whether they were fixed or modifiable. It could be argued that models stratifying factors according to whether they were HIV-specific or general might have been an appropriate method. In fact the overlap between the two stratifications was minimal, with age being the only non-HIV related factor included in the fixed category alongside other factors that were all HIV-specific.

4.3 Diet and Physical Activity Intervention

4.3.1 Principal Findings

This study aimed to investigate the effectiveness of a 6-month individualised diet and physical activity intervention on markers of insulin resistance in people living with HIV. Participants were given individualised advice in order to meet 10 diet and physical activity goals. On average, men achieved 4 goals and women 5. Most participants met or exceeded the goal to walk 10,000 steps per day. This level of achievement of goals was sufficient to result in a significant change in the primary outcome as well as many of the secondary outcomes.

The primary outcome was post-intervention change in glucose incremental area under the curve measured by a 3-hour frequently sampled liquid meal tolerance test, performed at baseline on Day 1 and post-intervention at 6-months. Post-intervention, the mean glucose incremental area under the curve measured in mmol x minute was 18% lower.

At 6 months, the mean insulin incremental area under the curve measured in units per minute was 31% lower. Baseline fasting glucose and insulin means were significantly lower at 6 months: reductions of 6% and 24%. Participants achieved significant reductions in mean weight, waist, percentage body fat, systolic blood pressure, triglycerides, 10-year cardiovascular risk, and a significant increase in mean HDL and life satisfaction score. Out of the 28 participants, only 6 achieved or exceeded the goal to lose 7% of body mass over the 6-month intervention period. However, the mean reduction of 4.1 kg was highly significant.

4.3.2 Markers of Insulin Resistance

The choice of Frequently Sampled Liquid Meal Tolerance Test (FSLMTT) for measuring the primary outcome was made in order to allow study of postprandial excursions of glucose and insulin as well as investigating the incretin effect. It was also chosen for practical reasons as it is less expensive to administer than the hyperinsulinaemic-euglycaemic clamp and less burdensome for participants. I also decided to extend the test from 120 to 180 minutes. To date searches have found no studies published or planned using the FSLMTT in HIV patients. The test has generated significant results, and demonstrated that glucose and insulin do not return to baseline levels within a two-hour period.

Graphs showing mean glucose and insulin excursions over the three hour FSLMTT (Figures 23 and 24 on page 147) suggest that the intervention had a different effect on glucose compared to insulin. The reduction in baseline glucose of 0.4 mmol/l is more or less consistent at each time point across the 3 hours. Post-intervention the postprandial glucose excursion at 30 and 60 minutes is moderately but not significantly less. With insulin, early phase secretion is statistically identical pre and post-intervention. However, insulin secretion from 30 minutes onwards shows a significant reduction comparing post to pre-intervention. This reduction in later phase insulin secretion may reflect the reduced requirement of insulin to achieve glucose disposal. Measured by Mari's method (Mari et al., 2002), the glucose disposal rate was 14% higher post intervention, increasing from 315 to 360 mmol/minute/m^2. There appear to be no clear changes in levels of incretin hormones that might explain changes in glucose or insulin dynamics.

It may be concluded that the intervention significantly reduced insulin resistance. The observed reduction in mean waist size, 36% reduction in fasting triglyceride levels and increased glucose disposal (oral glucose insulin sensitivity) rate measured by the Mari method support this theory. Additionally, exercise has been shown to improve skeletal muscle insulin sensitivity (Stanford and Goodyear, 2014). Increased physical activity levels observed across the pilot intervention might account for a component of the increased glucose disposal rate.

Although not measured, it is possible that the intervention mitigated levels of hepatic steatosis. Reduced ectopic fat would be associated with an improvement in hepatic insulin resistance with improved hepatocyte insulin sensitivity leading to suppression of glycogenolysis and gluconeogenesis, and promotion of glycogen synthesis and lipogenesis

(Farese et al., 2012). Improvements in hepatic insulin sensitivity and suppression of hepatic glucose production are associated with a reduction in fasting glucose levels (DeFronzo and Tripathy, 2009), a phenomenon observed post-intervention in this pilot study. These changes in hepatic function were not measured directly in this study and can only be inferred. Also not measured were C-peptide and glucagon. C-peptide is considered to be a more accurate surrogate marker of β-cell function than insulin (Tura et al., 2006). Additionally, measurement of glucagon levels could add information to future studies allowing a fuller understanding of the mechanisms leading to the observed reduction in both fasting glucose and incremental area under the curve.

Other intervention studies have demonstrated a clinically significant outcome through modest weight loss. In a study of a 16-week intervention in 8 participants with poorly controlled type 2 diabetes compared to 10 normoglycaemic participants, a reduction of 8kg achieved normoglycaemia in those with diabetes (Petersen et al., 2005). This was associated with a reduction in intrahepatic fat and an associated significantly reduced rate of hepatic glucose production. A future randomised controlled trial based on the intervention presented here could also measure intrahepatic fat in order to compare findings with previous studies.

Outside of HIV-specific research, a meta-analysis of diet and exercise intervention studies in people with prediabetes found a pooled effect size from 24 studies of a reduction in fasting glucose of 0.18 mmol/l (Appuhamy et al., 2014). The reduction in fasting glucose observed in the pilot intervention presented in this thesis (0.40 mmol/l) was outperformed in 3 of the 24 studies from the meta-analysis, and was considerably less than the intervention effect of a reduction of 1.6 mmol/l observed in the UK-based PREPARE study (Yates et al., 2009). Regarding BMI, 29 studies were included in the meta-analysis, and the pooled effect size was a reduction of 1.61 kg/m^2. This compares to a reduction of 1.41 kg/m^2 in the pilot intervention, outperformed by 14 of the 29 studies from the meta-analysis. Finally, the observed reduction of 10.4 mm Hg in systolic blood pressure from the pilot intervention compared to a pooled reduction of 2.8 mm Hg, outperforming all 23 studies included in the meta-analysis.

A study from the USA aiming to mitigate cardiovascular risk compared the effects of a 12-month highly intensive diet and lifestyle intervention with added metformin or placebo (Fitch et al., 2012). Participants (n=38) were HIV positive and had metabolic syndrome. At 12 months, fasting glucose levels in the intervention plus placebo group had increased by 0.17 mmol/l (3.1%) from baseline and in the lifestyle plus metformin arm had decreased by 0.39 mmol/l

(10.3%). In terms of secondary outcomes, in the US study lifestyle intervention alone resulted in an increase in mean waist and weight, whereas lifestyle plus metformin achieved mean reductions of 1.0% in waist and 3.2% in weight, considerably less than changes observed in the pilot study presented here.

Although given the differences in design and duration direct comparisons between the two studies cannot be drawn, it appears that the effect on fasting glucose of the pilot intervention presented in this thesis outperformed the 12-month intervention from the USA, but had a lesser effect compared to USA intervention plus metformin. It is unclear as to why the pilot intervention presented here would result in a greater reduction in fasting glucose, weight and waist compared to the US study, given the more intensive nature of both dietetic (weekly appointments) and exercise support (supervised gym instruction three times per week) in the US study. The US study recruited only those participants with metabolic syndrome, however 79% of participants in the pilot study presented here also had metabolic syndrome. It would appear that fasting glucose levels were lower in the US study, with a baseline mean reported as 5.47 ±0.17 mmol/l, compared to 6.13 ±0.75 mmol/l in this pilot study. This may partially explain the differences in intervention effect on glucose dynamics, although a more significant factor is undoubtedly the lack of weight loss seen in the lifestyle intervention arm in the US study. Changes in total daily energy intake were not reported in the US study. It is possible that historic exposure to ARVs may have differed between participants in the two studies, although 48.5% of participants in the pilot intervention presented here had been exposed to these ARVs. Exposure to ARVs associated with T2D has been demonstrated to have a complex interaction with glucose homoeostasis, with impaired peripheral glucose uptake, β-cell function, and hepatic insulin sensitivity resulting (Hruz, 2011). Lipodystrophy was not recorded as an exclusion criteria in the US study, and was not recorded in participant baseline characteristics, so may be a factor that could explain the difference in results.

There are few published studies detailing postprandial glucose and insulin excursions in HIV patients. In an Italian cross-sectional study of 84 HIV patients, 65 of whom were co-infected with Hepatitis C, 9 were found to have impaired glucose tolerance by OGTT (Gianotti et al., 2011). For these 9 participants, mean baseline glucose was 4.6 mmol/l, rising to 8.4 at 30 minutes and 8.9 at 120 minutes. Mean baseline insulin was 20.0 mIU/l, rising to 30.0 at 30 minutes, and 121.0 at 120 minutes. Pre-intervention curves presented in this thesis show different patterns compared to the Italian study. This might be due to the effect of Hepatitis C in that cohort with associated hepatic insulin resistance, fibrosis and other sequelae (Patel et

al., 2016); infectious hepatitis was an exclusion criteria for the pilot intervention presented here.

An investigation of leptin therapy in HIV patients (Magkos et al., 2011) measured postprandial glucose and insulin over 180 minutes. However, participants were treated with anti-diabetes medications and curves cannot be readily compared. As demonstrated in the results from the intervention presented in this thesis, the leptin study also shows return to baseline levels extending beyond 120 minutes to 180 minutes. Traditional OGTTs performed over 120 minutes may only partially describe dysglycaemia in HIV patients, with elevated glucose and insulin levels between 2-3 hours after the glucose or meal challenge missed.

Outside of HIV-specific studies, postprandial glucose and insulin curves have been measured following frequently-sampled OGTTs and liquid meal tests. In adolescents undergoing a FSLMTT, the glucose and insulin curves show excursions are similar in shape to those from this pilot study, although the return to normal levels appears to occur within 2 hours in adolescents compared to 3 hours in this study (Bacha et al., 2013). In an RCT investigating the effect of caffeine on postprandial glucose and insulin, excursions of both glucose and insulin were very similar in shape to those reported from the pilot study presented in this thesis, however in the RCT they returned to normal levels after 2 hours (Gavrieli et al., 2013).

In a study investigating the effects of non-glucose nutrients on insulin secretion in participants with prediabetes, those with IFG without IGT and those with IFG and IGT both experienced reduced postprandial glucose and increased postprandial insulin excursions with the mixed-nutrient liquid meal compared to a glucose-only challenge (Bock et al., 2007). In both cases curves returned to normal between 2 and 3 hours post-challenge, similar to findings from this pilot study. Investigators concluded that non-glucose nutrient-induced insulin secretion appears to remain relatively intact in those with prediabetes and could be secondary to the incretin effect. Examination of the pre- and post-intervention incretin curves from this study does not immediately suggest an explanation for the effect of the intervention on changes in glucose or insulin. It is counterintuitive that secretion of GLP-1 should be slightly elevated post-intervention, as secretion at 30 and 60 minutes post-liquid meal challenge has been shown to be lower in those with normoglycaemia compared to those with prediabetes (Vollmer et al., 2008). However it is possible that the observed increase in GLP-1 at 60 minutes post-intervention might be associated with suppression of glucagon secretion, although this was not measured in the pilot intervention.

Diet and Exercise

The intervention achieved a significant reduction in energy intake, with a mean reduction in energy balance of 475 kcal per day. However, using standard estimates that an energy deficit of 7,650 kcal is required to achieve a 1 kg loss of body fat (Stanton et al., 2006), with a mean loss of 4.1 kg over 180 days this would equate to a mean reduction of 175 kcal per day. This discrepancy can be attributed to at least two factors. Firstly participants may have experienced a reduction in lean body mass as well as fat mass over the 6-month period. A 55% smaller energy deficit is required for reducing protein stores compared to fat stores. Secondly, participants may have reported a reduced energy intake on completing the intervention.

On average, the contribution to total daily energy intake from carbohydrates did not change, whereas relative contributions from protein increased and fat and alcohol decreased. Participants reduced their intake of saturated fats by 22%. However, contrary to the design of the study, intake of monounsaturated fats also reduced by 17%, reflecting the reduction in total fat intake. In a dietary intervention for HIV patients in Brazil commencing ARVs for the first time (Lazzaretti et al., 2012), intake of monounsaturated fats increased proportionately at the expense of saturated fats. It could be argued that given the overall positive impact on insulin resistance of the pilot intervention as a whole, the goal to maintain intake of monounsaturated fats has been shown to be unimportant. However, there is a strong evidence base for the importance of monounsaturated fat intake for general health including reducing postprandial hyperglycaemia (Bozzetto et al., 2016), and additionally given the high prevalence of hyperlipidaemia in HIV (Ballocca et al., 2016). How to achieve maintenance or increase of monounsaturated fats will require consideration in the design of future interventions in this patient group.

Advice to increase intake of wholegrains was successful with a mean 41.4% of carbohydrate intake comprised of wholegrains at 6-months compared to 13.2% pre-intervention. Intake of fibre as a whole also significantly increased. Prior concerns that an increase in fibre and wholegrain intake might adversely affect gastrointestinal problems relatively common in PLWH (Neuman et al., 2012) were unfounded. There was no statistically significant change in mean gastrointestinal symptom score, bowel frequency or Bristol stool chart score.

Significant changes were observed in sodium intake with a mean reduction of 21%. Calcium and iron intakes also fell, although these reductions were not statistically significant. Reduction in sodium was one of the 10 intervention goals set for participants, therefore this significant

result is a measure of success. However, maintenance of calcium intake was a stated aim within the study protocol, and although the reduction in calcium observed over the intervention was not statistically significant, this result may influence design of future dietary interventions in PLWH.

Analysis of sodium, calcium and iron intakes should be treated with caution, however, as 5-day diet diary analysis used in this pilot study is unlikely to provide sufficient data to provide a high level of accuracy (Bingham et al., 1994). Future studies may wish to include measurement of validated biomarkers (Prentice et al., 2011), for example urinary sodium, to increase accuracy of assessment of change in salt, mineral, fruit and vegetable intake, particularly where attempting to characterise factors associated with changes in blood pressure and other secondary outcomes.

It may be clinically relevant for future trials in PLWH to focus on maintaining or increasing calcium and iron intake given the high burden of bone disease and anaemia in this patient group (Peters et al., 2013b). Additionally, future studies may wish to estimate adherence to the Mediterranean diet utilising a scoring system or food-frequency questionnaire approach (Estruch et al., 2013).

4.3.3 Strengths and Limitations

The pilot intervention was comprised of standardised goals to achieve. Advice to achieve these goals was individualised. This approach could be translated into clinical practice, as it mirrors the individualised approach taken by health care practitioners (Nybacka et al., 2011, Karagiozoglou-Lampoudi et al., 2012). The support offered to participants in the pilot intervention presented here was less intensive in nature than other interventions in PLWH. However, 6 personal appointments with a dietitian over a 6-month period may prove too expensive to implement widely, and investigation of less expensive treatment options may be warranted.

Participants were eligible for the intervention if they presented with IFG (fasting glucose 6.0-6.9 mmol/l), the same definition used to classify prediabetes in the phenotype study. When comparing the 33 intervention participants with the 55 phenotype study participants with prediabetes, the groups were largely similar. However, the intervention group had a

significantly higher BMI (30.7 vs 28.8 kgm^2) and higher rates of hepatic steatosis (63.6% vs 46.6%). This difference may limit confidence in translating the effect of the intervention to those with lower BMIs and those without hepatic steatosis. A larger study could test this effect.

A limitation regarding methodology was potential bias from performing measurements and analysis of results. As far as possible, measurements such as blood pressure and weight were performed by the research nurse from the Clinical Research Facility, rather than by me. However, we were both aware if the research appointment was baseline or post-intervention. As per protocol, certain measurements were used as motivators for participants. These included baseline and mid-point lipids, and monthly weight and waist measurements. Analysis of questionnaire data and glucose and insulin samples was delayed until the final participant had exited the intervention. However data was analysed by me, cognisant of baseline or post-intervention. In my opinion it is possible that bias may have occurred but would be unknowing and limited. Future study design should include measurement and analysis blinded to baseline or post-intervention, performed by a researcher not involved in delivery of the intervention.

4.4 Qualitative Research Investigation

4.4.1 The Study Population and Interview Details

Sampling:

The aim of recruiting a sample to represent the diversity of the cohort was partially met. The age range of those with prediabetes was reflected by those interviewed, as were ethnicity, socioeconomic status and sexuality. However there were clear difficulties in representing gender at interview, with 27% of women invited consenting to participate in the in-depth interviews, compared to 69% of men. Investigators in Canada found that the principal barriers to recruiting women living with HIV to research studies were, in order of importance, the sensitivity of the research subject followed by availability and logistics, language barriers and fear of disclosure of HIV status, with half of participants citing these barriers (Loutfy et al., 2014). However, 40% also mentioned lack of trust in study personnel as a barrier. It is probable that this was a factor in this study although it is not possible to quantify any effect.

Data saturation was only partially achieved when the final participant exited the intervention. Ideally, recruitment to interview should have continued for those of non-White ethnicities, and for those who declined to participate in the intervention but agreed to interview.

Those who declined to participate were challenging to recruit to interview. This perhaps is not surprising as potential participants were in effect being asked twice to participate, having already declined when asked first. The ethics of this aspect of study design had been questioned by members of the Research Ethics Committee. The rationale was to investigate whether barriers to participation and barriers to behaviour change may be interlinked. Recently, other studies have attempted to investigate reasons for non-participation in lifestyle interventions (Normansell et al., 2016, Attwood et al., 2016). Researchers here also report great difficulty in recruiting those who have declined participation in trials. It could be argued that participants who agree to interview might not be representative of the larger group who decline intervention participation. With this limitation in mind, the typologies described in Table 3.36 suggest that those who declined to participate share characteristics with those who performed poorly in the intervention.

Certainly, almost all of those interviewed had been living with HIV for a long duration and reflected either the metabolic and health legacy of suboptimal HIV treatment or presentation of HIV late in the course of disease progression. In this regard findings from the interviews may reflect experiences from a more health-challenged group of people living with HIV. However, this reflects those people living with HIV most at risk of developing Type 2 diabetes.

Conduct of the Interviews:

Interviewees were offered a choice of interviewers: myself (male, White) or a Health Advisor (female, Black African origin). Those invited to interview who had not taken part in the intervention may have had no or limited previous clinical contact with me, or may have been involved in a professional relationship of varying duration. Those who had participated in the intervention in addition to working closely together over the 6-month period may also have been involved in a prior professional relationship of varying duration. None of the 23 interviewees chose to be interviewed by the Health Advisor. Those who had experienced a longer duration of professional relationship with me may have felt less able to choose an alternate interviewer. However those who had no or limited prior contact also chose me to conduct the interview.

There were benefits and disadvantages to conducting the interviews myself. Benefits included a depth of knowledge and experience regarding diet and exercise behaviours, and for those interviewees who had participated in the intervention, a close knowledge of events and behaviours. Disadvantages included an increased likelihood of interviewees feeling less able to voice concerns about the management of the intervention delivered by me, and the potential for interviewees to talk about issues they perceived might please me. Care was taken throughout to distinguish between my usual clinical interviewing role and this research interviewer role, and to position the interviewees themselves as experts (Hunt et al., 2011).

On reflection and re-examination of interview transcripts I have observed several examples of interviewees clearly attempting to praise my efforts:

> "I don't want to disappoint myself, yeah, but I didn't want to disappoint you either because I know how much effort and time you put into this". [Interviewee No. 15, female, aged 42].

I have also observed examples where those interviewees with whom I had a prior professional relationship felt able to ask questions or make statements in a direct manner:

> "Do you worry about your weight, being a dietitian? I know you're meant to ask me the questions". [Interviewee No. 23, male, aged 41].
>
> Interviewer: "Did you get enough support?" Interviewee: "From you? Did I get any support from you? I can't remember". [Interviewee No. 2, male, age 64].

The study protocol dictated offering a choice of interviewers, therefore it was not possible and potentially unethical for the Health Adviser alone to conduct a sample of interviews in order to compare the effect of prior relationship with interviewees.

4.4.2 The Acceptability of the Intervention: Process Evaluation

It was hypothesised that future interventions could be informed by an evaluation of the acceptability of the intervention. From my literature search, no investigations of the acceptability of diet and exercise interventions in PLWH have been published to date. The

intervention was largely acceptable to participants. Those who declined to participate cited a range of reasons to explain their decision. However, in terms of the acceptability of the intervention these were limited to two areas: burden of attending for research visits and unease with the 3-hour frequently sampled liquid meal tolerance test.

Participant Information Sheet:

During design of the study efforts had been made to make the participant information as accessible as possible, responding to reports that graduate-level reading skills were required for understanding participant information materials in HIV research studies in the UK (Collins et al., 2015). The participant information leaflet for this study was assessed for readability, scoring 67 on the Flesch-Kincaid scale, indicating fair ease of readability. Although comments were made regarding their ease of accessibility by some interviewees, others commented on their complexity and admitted to skim-reading or avoiding reading materials altogether. It is a requirement that consent to participate in research studies is fully informed (Health Research Authority, 2015). Future participant information materials should be developed with this in mind.

Frequently-sampled Liquid Meal Tolerance Test:

Interviewees who experienced this 3-hour test were divided in opinion. Most found it straightforward, others found it challenging but had prepared for this after reading the information leaflets. Another group struggled with tolerance, citing discomfort, pain and unhappiness at the duration and amount of blood taken. Those who declined to take part in the intervention expressed unease with this test, suggesting this as a contributing factor to non-participation. One interviewee who declined the intervention also described an inability to fast for the test.

More invasive tests such as the hyperinsulinaemic-euglycaemic clamp are routinely used in research and found to be scored as a moderate or high barrier to participation in 24% of potential participants compared to 35% concerned about missing work (Robiner et al., 2009). Participant information leaflets for future studies using the frequently-sampled liquid meal tolerance test should clarify the relative ease of administration and low burden of the procedure, and clearly define the amount of blood taken across the test.

Participant Literature:

Questionnaires were acceptable, with some participants describing them as fun and a distraction from the 3-hour tolerance test. The 5-day food diaries were acceptable and useful as a monitoring tool for most participants. However, some participants felt diary completion was a burden. Future studies should consider alternatives to written food diaries, for example apps using photography of foods eaten.

Intervention Design:

The overall design was acceptable. Most participants preferred the structure of monthly appointments over a 6-month period to other options discussed. Suggestions were made for more or less frequent appointments over a 6 or 12 month duration with alternative technologies supporting adherence to the intervention. Clearly a flexibility of approach should be incorporated into future design as recommended in UK guidelines for diabetes prevention and behaviour change (NICE, 2012, NICE, 2014a).

Support:

Flexibility of support was recommended by interviewees. Pedometers were highly valued as a tool to aid increasing physical activity and gym groups were suggested as an alternative.

The high rate of acceptability of the intervention with practical suggestions for future design mirrors findings from other published process evaluations in diabetes-related lifestyle interventions (Feathers et al., 2007).

4.4.3 Enablers and Barriers, Identity and Control

Enablers and Barriers:

Certain enablers and barriers to change in diet and exercise habits may be HIV-specific in nature and others general. General enablers and barriers elicited from a narrative literature review (Table 1.11 on page 52) can be compared to findings from interviewees.

In summary, self-confidence and optimism were key to successfully achieving goals. A belief that lifestyle change could reduce disease risk and a desire to prevent diabetes had a positive impact. Societal pressure to lose weight, improved knowledge and skills, overcoming isolation,

commitment to succeed and a desire to tackle obesity were strong enablers. Planning, a stepwise approach and use of a pedometer as a tool to monitor achievement of goals were enablers. Those who felt that HIV was largely controlled and a lesser health burden compared to diabetes and avoiding adding to pill burden were motivators to change.

Societal valorisation of obesity in African cultures and among gay men identifying as bears, lack of support, conflicting advice, pressures at work or home, bad weather and lack of willpower were all significant barriers to change. Healthier foods were perceived to be more expensive. Those who felt diabetes was a lesser health concern compared to HIV were less motivated to change behaviours. Thinness may be associated with AIDS and this fear of disclosure of HIV status or association with memories of AIDS acted as a barrier. Lifestyle change was considered futile given the legacy of HIV and associated medicines.

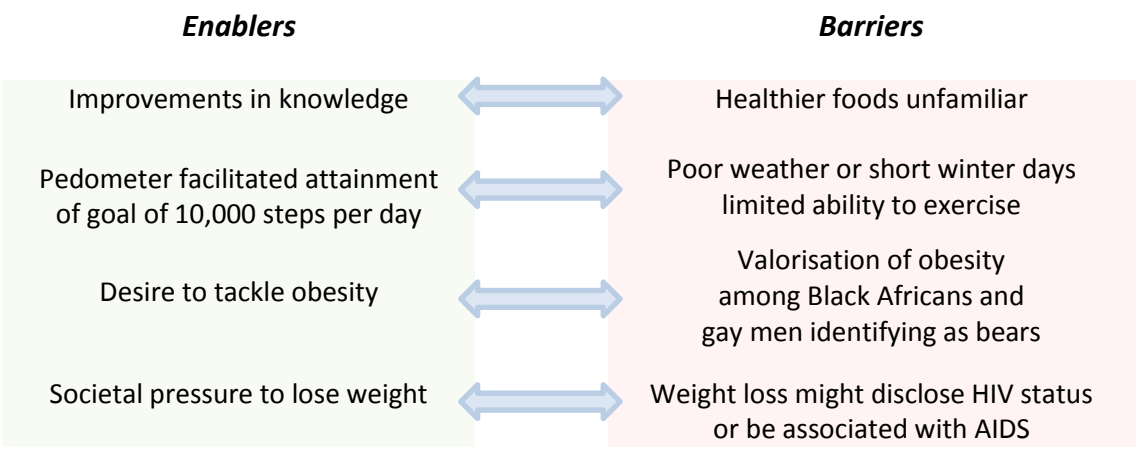
Typologies:

The typologies described in Table 3.36 suggest that those who declined to participate share characteristics with those who performed poorly in the intervention. Both groups appeared to have an external health locus of control, blaming HIV medicines and social pressures for inability to change or participate in the intervention. Individuals from both groups were isolated, and prioritised HIV over other health issues, for example prioritising keeping HIV secret. When asked about future intervention design, participants within this typology suggested daily support from dietitians regarding dietary change and provision of a personal exercise coach might help them achieve goals. This contrasts with those who performed well in the intervention who were characterised by an internal health locus of control. The external health locus of control associated with inability to adopt lifestyle change parallels that described among people with serious mental health challenges (Pearsall et al., 2014). However, poor mental health was widespread among participants in the study presented here and was not a barrier to change or a factor closely associated with inability to take control of health risk. The typologies suggest attitudes to loss of identity may differentiate between those who performed well or poorly in the intervention. This loss of identity refers particularly to people of African origin and also gay men who identify as bears.

Tensions between Data

Health locus of control and prioritisation of health-related issues may explain tensions observed in the analysis of interview data (Figure 27).

Figure 28: Tensions Between Enablers and Barriers



Participants cited improvements in their knowledge as a powerful enabler to behaviour change. For example, understanding of food labelling helped participants choose lower fat and reduced salt options. However, despite improving knowledge regarding healthier foods, participants who did not change behaviours cited these foods' unfamiliarity as a barrier. In effect, they were prioritising continuing to consume less healthy usual foods over reducing diabetes risk. Similarly, participants discussed at length the utility of the pedometer as a facilitator to achieve walking targets. However, those participants who struggled to achieve targets exhibited an external health locus of control, blaming poor weather or short winter days. Those who prioritised overcoming these barriers, for example by exercising at home or elsewhere indoors, achieved or exceeded physical activity goals.

A desire to tackle obesity to reduce diabetes risk, and an acknowledgment of societal pressure to lose weight were apparently at odds with valorisation of obesity among certain groups and fear that weight loss might disclose HIV status or be associated with ill health. However, those participants of Black African origin and gay men identifying as bears who achieved weight loss goals prioritised reducing diabetes risk over these barriers.

Lessons learnt from examination of these tensions can be used to inform clinical work as well as future research interventions.

Comparison with Published Findings

General enablers and barriers elicited from this study mirror those found in reviews of enablers and barriers to diet and exercise change in people at risk of developing type 2 diabetes (Korkiakangas et al., 2011, Morrison et al., 2014), those with cardiovascular disease (Murray et al., 2013), African-origin cancer patients (Oyekanmi and Paxton, 2014) and gay men identifying as bears (Moskowitz et al., 2013).

Compared to other studies investigating lifestyle change in those at risk of diabetes through in-depth interviews or video recordings of group sessions, there were no different general enablers or barriers. However, the relative frequency or importance varied. There were few health-related barriers in a study of adults at high risk of diabetes with a mean age of 49 years (Korkiakangas et al., 2011), contrasting with the frequent reporting of health-related barriers in the HIV cohort presented here. Barriers in a study of South Asian-origin people living in Scotland cited poor weather and employment and domestic commitments as the major barriers to change (Morrison et al., 2014).

In this HIV cohort, isolation was a major barrier to change and a feature common to those declining to take part. Those who were able to seek support tended to achieve more goals during the 6-month intervention. Isolation is increasingly recognised as an important concern relating to poor health among older adults in the UK (Nicholson, 2012). It could be argued that isolation in this cohort has an HIV-specific component secondary to HIV stigma and the high rates of poor mental health seen among people living with HIV in the UK (Blashill et al., 2011).

This HIV cohort has a high burden of comorbidities. Investigators in the USA conducted in-depth interviews with people with chronic comorbid conditions including diabetes, arthritis, hypertension, breathing and musculoskeletal problems, and found several barriers specifically related to having multiple comorbidities including severe breathing issues and effects from polypharmacy (Bayliss et al., 2003). These findings are similar to multiple health issues and pill burden mentioned by interviewees in this HIV study.

Comparing this HIV cohort with obese breast cancer survivors in the USA (Oyekanmi and Paxton, 2014), there are clear differences in barriers to lifestyle change. The cancer survivors reported few health-related barriers. Indeed the main barriers cited were lack of support, time, self-confidence and company, and fear of injury from being unfamiliar with exercising. There were more similarities compared to colorectal cancer survivors (van Putten et al., 2016),

where a range of condition-related barriers limited lifestyle change. These included chemotherapy side-effects and body image issues related to stoma care. These findings resonate with HIV-specific barriers elicited from this study.

In an investigation of diet and exercise change in HIV positive individuals in the USA, focus groups were used to elicit barriers and enablers (Capili et al., 2014). The principal barriers in the cohort studied were financial, cultural unfamiliarity with healthier foods and exercise, lack of support, lipodystrophy and weight gain to mask HIV-related illness. This study mentions only in passing deliberate weight gain to mask HIV. This is perhaps less of a significant factor than expressed by interviewees in the study presented in this thesis. Facilitators were knowledge, group support and a positive attitude to change. These enablers and barriers were also prominent in the HIV study presented here.

This study presents HIV-specific enablers and barriers not elicited in other published studies. These enablers and barriers may be related to diabetes risk, including the perceived relative health concerns of the two conditions and the enduring belief of the futility of lifestyle change given the legacy of HIV infection and HIV therapies.

The fear of disclosure of HIV status should not be underestimated, affecting research participation and desire or ability to change behaviour. Participants felt happy to disclose development of diabetes but not HIV. This mirrors findings from a study in South Africa where participants with HIV and tuberculosis coinfection were open about their tuberculosis infection but not HIV (Daftary, 2012).

It is important to consider an absence of the consideration of ageing by participants in this study, where the mean age of interviewees was 55 years. Age is significantly correlated with diabetes risk in people living with HIV, as indicated in this thesis and in other studies. The only reference to ageing by any interviewee was regarding central obesity:

> "I'm at that sort of age where you get a gut anyway. You know, I don't see it as being a big deal". [Interviewee No. 12, aged 63].

Interviewees made no mention of the link between age and diabetes risk. This contrasts with the strength of belief regarding a link between HIV medications and diabetes risk.

Studies have investigated the valorisation of obesity in people of African origin in Africa itself, in the USA and in the UK. In West Africa, women state the desire to decrease weight but do

not do so due to social valorisation (Cohen et al., 2013). In Black Americans there has been reported a significant misperception of weight, particularly among women, when compared to White Americans (Hendley et al., 2011). In this study based in Atlanta, Black Americans were significantly less likely to classify themselves as obese. Among HIV positive American women, a significantly higher percentage of Black women wished to be heavier compared to others (Clark et al., 1999). There was no significant difference between ethnicities in the belief that higher BMIs masked illness. In the UK Black British women are more accepting of larger body sizes than White women (Shoneye et al., 2011). Studies of Black African women in the UK suggest that migrants retain valorisation of overweight, whereas second generation Black Africans' perceptions of body image are similar to White Britons (Tovee et al., 2006, Swami et al., 2012). A small UK study of HIV positive women found that Black African women were more satisfied with being overweight than White women (Bradbeer and Bakar, 2008).

In the study presented in this thesis, interviewees discussed valorisation of overweight in the African community. Those African participants who performed well in the intervention had no issue with losing weight and did not associate this with loss of identity, contrasting with those who did not perform well.

Gay men who identify as bears have not been extensively studied and to date there is no published research regarding HIV positive bears. A comparison of 469 men who identify as bears compared with gay men who do not suggests that bears are significantly heavier (Moskowitz et al., 2013). In the study presented in this thesis weight loss presented a loss of identity for gay men identifying as bears. It is not known if this is specific to those living with HIV.

In the general non-HIV population internal health locus of control has been associated with healthier diet and exercise habits (Cobb-Clark et al., 2014), consistent with findings from this study. A meta-analysis suggests that people of African and Asian origin exhibit a greater external health locus of control compared to those from Western White cultures (Cheng et al., 2012). This is believed to be related to a holistic approach to health among Asian communities and a collectivist approach common in Africa, contrasting with a belief in Western society that health determinants are individual and broadly causal. An internal health locus of control has been associated with lower socioeconomic status (Grotz et al., 2011). An analysis of health locus of control in this study, differentiating by participants' ethnicity and socioeconomic status is not possible within the qualitative research design used. However, future

investigations may wish to explore the possibility of this relationship on order to maximise clinical application.

Future studies should consider inclusion of tools to assess satisfaction with body shape, and perception of body image. A short 10-questions body appreciation scale has been developed and validated for use with UK-based populations (Swami et al., 2012). Given the high level of dissatisfaction with body image expressed by HIV positive women and men in the USA (Sharma et al., 2007, Sharma et al., 2006) use of this scale in clinical practice would also be warranted.

The finding from this study that those who declined to participate in the intervention share characteristics with those who performed poorly in the intervention may have implications for other lifestyle behaviour change programmes. In this study both groups demonstrated an external health locus of control, prioritisation of issues other than diabetes risk, and an absence of or a limited support network. This might suggest that these issues require exploration and resolution, for example through clinical psychology or counselling, prior to embarking on an intervention.

4.4.4 Research Participation

Two frequently-mentioned enablers to participation in HIV research included altruism and the opportunity to potentially improve one's own health, particularly driven by a fear of developing other illnesses when already dealing with the consequences of HIV. Altruism as an enabler to research participation may not be entirely selfless. Investigators have observed that even where altruism appears to be genuine, research participation could plausibly advance the participant's wellbeing, for example where the research endpoint may be beneficial directly to themselves or their community (Largent, 2016).

Being approached by non-clinical staff to introduce ideas regarding research participation and reimbursement of travel expenses were also cited as enablers. The principal barrier to participation identified irrespective of gender, ethnicity or active research participation was the potential for breach of confidentiality and disclosure of HIV status. Other barriers included logistic constraints, a lack of knowledge regarding research in general, poor communication particularly in terms of printed materials, ill-health, lack of feedback of results and a concern that participation in HIV-related research would be a constant unwelcome reminder of status.

Stigma has been an issue central to people living with HIV since the start of the epidemic (Blashill et al., 2011). People with HIV remain highly concerned regarding confidentiality and disclosure of HIV status. This has the potential to impact negatively on research participation.

4.4.5 Research Quality and Future Directions

This is the first research study investigating the attitudes and beliefs of people living with HIV at risk of developing type 2 diabetes. A key strength of this qualitative study was the inclusion of interviewees who declined to take part or were withdrawn from the intervention in addition to those who completed the 6-month programme. Having the dual role of intervention facilitator as well as interviewer allowed insights into progression through the programme to inform probing questions during the interviews. Interviewees were relaxed and open in their communication. On reflection, my concerns regarding the potential for lack of objectivity were unfounded. Other researchers have suggested that the intimacy and familiarity experienced by anthropologists in particular helps catalyse the experience (Charmaz, 2004). I agree with this view and feel that the familiarity between me and participants resulted in the generation of important and significant data, for example issues regarding gay men who identify as bears.

Limitations included fewer women participants than expected. No participants opted to be interviewed by the alternate to me. There was potential for the interviews to be adversely affected by the Hawthorne effect (McCambridge et al., 2014) where research participation itself affects behaviours:

> "I don't want to disappoint myself, yeah, but I didn't want to disappoint you either because I know how much effort and time you put into this". [Interviewee No. 15, female, aged 42].

Future research may consider inclusion of focus groups in its design. Focus groups have been used effectively in research involving people living with HIV, although participants highly concerned about confidentiality may choose to decline attending groups (Capili et al., 2014).

Future research should also consider recent migrants to the UK where the principal barrier to participation is language (Ochieng, 2013). Barriers to recruiting to health research in London have been characterised as difficulties in travel logistics and language barriers (Newington and Metcalfe, 2014). Future study design should take these factors into consideration.

4.5 Recruitment

Challenges to Recruitment

Across the three interrelated studies presented in this thesis a total of 339 patients participated. Posters advertising the study placed in clinic waiting areas had limited success in terms of potential participants self-referring, although the effect of posters raising awareness among patients or staff was not measured. A total of 2,934 patients were identified through outpatient clinic lists or medical records, or self-referred. Prior to screening, 967 patients declined any research involvement or did not respond to an invitation to participate, and at screening a further 821 declined to take part or did not respond to invitation. Good practice guidelines were followed; patients were not asked to divulge reasons for declining participation (Health Research Authority, 2016). However, among those who volunteered reasons the commonest were: research fatigue (38%), problematic logistics (34%) and a lack of interest in research (14%).

I was unable to recruit any participants aged less than 22 years or those who had acquired HIV through vertical transmission. This may have been be due to research fatigue, a phenomenon reported in younger PLWH (Pagano-Therrien, 2013) where over-researching has been linked with challenges to recruitment. This has also been reported in lifestyle interventions where 17% of participants declining a diabetes prevention programme cited research fatigue (O'Dea et al., 2013). Investigators leading a qualitative research study suggested that increasing apathy, financial barriers and a lack of underlying support can drive research fatigue (Clark, 2008). In a London-based study, investigators interviewed health researchers regarding barriers to participation (Newington and Metcalfe, 2014). The two principal barriers cited were travel distance and language.

Recruitment of women to this study was challenging, particularly women from non-White ethnicities. This had been anticipated based on published reports from other studies of people living with HIV, for example a Canadian study where investigators interviewed research site coordinators regarding the participation of HIV positive women in trials (Loutfy et al., 2014). The purposive sampling method used for the cross-sectional study ensured that women were represented in that study. However, regarding the intervention and qualitative studies, I was unable to recruit a representative sample of women participants.

Selection Criteria

The principal reasons for exclusion of potential participants from the phenotype study were being unable to provide informed consent (31% of those excluded) and being unable to communicate in English (also 31%). It has been recommended that efforts should be made to overcome language barriers in health research in the UK (Ochieng, 2013), and this should be considered in the design of future research projects.

Reasons for exclusion from the intervention were: unable to commit to a 6-month programme (33%), infectious hepatitis (28%), use of medications associated with dysglycaemia (17%), naïve to ARVs (17%) and potential for pregnancy (5%). The effectiveness of the pilot intervention could have been compromised by liver impairment or use of medications associated with dysglycaemia. Together with excluding participants unable to commit to the 6-month programme, these exclusion criteria remain justified. However, future interventions may wish to include those naïve to ARVs.

A major theme from the process evaluation conducted using data from in-depth interviews was inclusion of a more flexible intervention design in future studies.

In the intervention the attrition rate of 1 participant from 29 (3.5%) is very low compared to a diet and lifestyle intervention in HIV patients in the USA (Fitch et al., 2012). In that study, 36 out of 50 participants completed the 12-month intervention. Six-month attrition rates were not published therefore a direct comparison cannot be made.

5 CONCLUSIONS

> *'people living with HIV present with particular barriers to change, and future interventions must address these to improve efficacy'*

The epidemics of obesity and type 2 diabetes in this HIV cohort mirror the general population with HIV no longer a condition associated with wasting. Comorbid disease burden could be reduced by screening for dysglycaemia in HIV clinics and proactive prevention and treatment of obesity. The effectiveness of the pilot intervention demonstrates the potential to reduce risk for type 2 diabetes in HIV. However, the qualitative research presented here suggests people living with HIV may experience particular barriers to change and future interventions must address these to improve efficacy.

5.1 The Phenotype of Dysglycaemia in HIV

Historically HIV was a disease associated with wasting and premature death and therefore conventional risk factors for dysglycaemia such as age and central obesity were of little relevance. However, PLWH are now living longer, and wasting is very uncommon. Data from the phenotyping investigation has demonstrated significant trends among this ageing HIV cohort, suggesting that the rates of overweight and abdominal obesity among PLWH are increasing and are now comparable with the general population. Participants of non-White ethnicities experienced a particularly high rate of obesity. Coupled with an increasing prevalence of hepatic steatosis, hyperlipidaemia and hypertension, the burden of comorbid disease suggests the development of a screening, prevention and treatment programme is warranted.

Type 2 diabetes is highly prevalent in this diverse London-based HIV cohort, and as in the general population, there is a significant correlation between diagnosis of prediabetes or type 2 diabetes and increasing weight and age. As observed in the general population type 2 diabetes in this cohort was associated with significant socioeconomic deprivation. As with studies of other HIV cohorts, dysglycaemia was correlated with HIV-specific factors including duration of HIV infection, degree of weight gain following initiation of anti-HIV medications and lipodystrophy. However, regression analysis suggests that rather than these HIV-related factors, it is the modifiable factors hepatic steatosis and hypertension that contribute the greater association with diabetes risk in this HIV cohort. These findings give impetus to moving forward with developing diabetes prevention strategies based on diet and exercise interventions which through weight loss can mitigate both hypertension and hepatic steatosis.

5.2 Prevention of Type 2 Diabetes in HIV

The pilot intervention has demonstrated the potential for dietary change, increased physical activity and weight loss to reduce diabetes risk in people living with HIV. This intervention resulted in a greater treatment effect compared to a more intensive diet and exercise intervention in PLWH studied in the USA, and comparable or greater treatment effects compared to pooled results from a meta-analysis of lifestyle interventions in participants with prediabetes from the general population. The underlying mechanisms at the heart of the intervention were not measured. Future studies should assess these, e.g. measurements of the degree of fatty infiltration in the liver. However, despite the significance of mean treatment effects participants demonstrated a range of success achieving intervention goals.

The in-depth interviews provided a greater understanding of the success or otherwise of participants in the intervention. This qualitative research suggests that people living with HIV may present with particular barriers to both participation in clinical research and to adopting lifestyle change. Fear of disclosure of HIV status and worries about confidentiality were common themes. Common to those who declined to take part in the pilot intervention and those who achieved few intervention goals was an external health locus of control. Diabetes risk was blamed on HIV and antiretroviral medicines as well as social pressures, and type 2 diabetes was seen as a lesser concern compared to HIV. A loss of identity, particularly among African-origin participants and gay men identifying as bears, was a theme common to those achieving fewer intervention goals. In contrast, those who performed well in the pilot

intervention exhibited an internal health locus of control, taking responsibility for their diabetes risk. Common to those achieving more intervention goals was a support network, either well-established or proactively constructed early in the programme. Given the range of achievement of intervention goals, findings from the in-depth interviews should be incorporated into future design of and approach to behaviour change programmes for people living with HIV. For example, an assessment of health locus of control might warrant counselling or psychology support prior to initiation of lifestyle change. For those who continue to view diet and exercise change as futile, alternative treatments including pharmacological interventions might be considered.

5.3 Clinical Implications

In my investigation no participants under the age of 39 were diagnosed with prediabetes or type 2 diabetes. This might suggest that clinical screening for diabetes risk should be targeted at those approaching and over the age of 40. Additionally, enhanced screening for diabetes risk in HIV patients should be considered. Extended screening of risk factors might include directed screening for hepatic steatosis in at-risk individuals. Appropriate interventions, including preventative measures, might extend beyond the management of modifiable risk factors by means of dietary and exercise advice. For example, health care practitioners might favour use of those ARVs with less effect on insulin resistance in those presenting with prediabetes or type 2 diabetes, and also those with significant risk factors.

Particular attention may be directed to those initiating antiretrovirals for the first time. Demonstrated in this study and in research elsewhere is the increased risk for comorbid metabolic disease in those experiencing weight gain following initiation of ARVs. Prevention of weight gain at this time may prove a valuable investment for future health. Counselling to change diet and exercise is especially relevant to PLWH given low levels of physical activity and fruit and vegetable consumption and high prevalence of overweight and obesity compared to the general population. The beneficial effects of lifestyle change on a range of parameters demonstrated by adherence to the intervention can be applied clinically. Findings from the qualitative study can be used to improve clinicians' understanding and support when counselling to change diet and exercise behaviours in PLWH.

5.4 Future Research

A Randomised Trial is currently being developed with PPI input aiming to investigate the prevention of obesity-related comorbidities in HIV. The current design focuses on comparing the individualised diet and physical activity advice approach developed in the pilot intervention presented in this thesis with a less intensive approach employing distance support. It is anticipated that this RCT will be powered to enable a regression analysis of the contribution of individual components of the intervention to the primary outcome. However, eligibility criteria will require careful consideration given the recruitment challenges experienced in the studies presented in this thesis, and the inherent difficulties of scaling up into an RCT.

The relationships between deliberate weight loss and fear of disclosure of HIV status, loss of identity for those of African origin, and loss of identity for gay men identifying as bears need further exploration.

People living with HIV are facing increased risk of type 2 diabetes, cardiovascular disease, osteoporosis and chronic kidney failure. In HIV, common factors contribute to the development of these conditions associated with ageing. Development of a unified screening tool would aid targeting of resources.

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7 APPENDICES

7.1 Recruitment Advertising

7.2 Participant Information Sheet and Consent Form

Prevention of Type 2 Diabetes in HIV: A Pilot Study of Effectiveness and Acceptability (the "STOP Diabetes in HIV" study)

My name is Alastair Duncan, and I am a dietitian and researcher at Guy's and St. Thomas' Hospital. I am inviting you to take part in a research study. The results of the study will be used to see if an approach shown to prevent Type 2 Diabetes in the general population can work with HIV positive patients. As part of this study we are trying to find out if there are any particular risk factors for developing diabetes. I have overall responsibility for this study, and my contact details can be found towards the end of this information sheet.

Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. If you decide to take part, this part of the study will involve you attending the Harrison Wing clinic for a single 30 minute visit, where you will be asked some questions, and have some measurements taken. You might be asked to have a single blood test to check your blood sugar level. In addition, we will check your medical records to find information relevant to the study. Further details can be found below.

Please take time to read the following information carefully as it will explain the study, together with what you will be asked to do if you take part, in more detail. Please talk to others about the study if you wish. You could ask at the clinic reception desk to speak with your patient advocate. Ask any of us if there is anything that is not clear or if you would like more information. Take all the time you need to decide whether or not you would like to take part in the study.

What is the purpose of the study?

Type 2 diabetes is a condition where the body cannot use energy from food properly any more, and there is a risk of sugar building up in the blood. High levels of sugar make the blood thick and syrupy and this can go on to cause dangerous health problems if not treated. People with HIV are believed to have a higher risk of developing type 2 diabetes when compared to HIV negative people of the same background, age and size.

This might be because of a combination of three factors:

- HIV infection causes inflammation within the body, which does not go away completely even when the virus is well controlled by medication
- Some medicines for controlling HIV may increase the risk for developing type 2 diabetes
- Many people living with HIV are overweight these days, and this is well known to increase the risk for developing type 2 diabetes in HIV negative people.
-

In the study, we will ask some questions and take some measurements to find out if people living with HIV have risk factors for developing type 2 diabetes. We are aiming for 338 people to take part in this risk factors study, and we will sort everyone, including you, into one of 3 groups:

1. People with normal blood sugar levels
2. People with slightly high blood sugar
3. People who already have diabetes

The information we will get from this study will be used to design a much larger research trial investigating prevention of type 2 diabetes in HIV. It will also help healthcare providers, like your doctor, dietitian or nurse, look out for people at risk of developing diabetes.

Why have I been chosen?

You have been chosen because you have been diagnosed as HIV positive, you have been receiving care for this condition at Guy's and St. Thomas', King's College Hospital, or Beckenham Hospital, and one of three other factors:

1. You have normal blood sugar
2. Your blood sugar is a little higher than usual, sometimes called "impaired fasting glucose"
3. You have diabetes

If you are in group 2, and your blood sugar is a little higher than usual, this is known to indicate a risk for going on to develop Type 2 Diabetes in the future. If you have not already discussed this condition with your GP or routine clinic doctor, you may wish to do so at your next appointment.

Do I have to take part?

No. It is completely up to you to decide whether or not to take part in this study. If you have any questions about the study, you can contact the Investigator Alastair Duncan (telephone number at the end of this Participant Information Sheet) or ask your nurse, doctor or any clinician at a clinic visit, or you can chat with your patient representative. After you have had all your questions answered and have decided to take part in the study, you will be asked, at the clinic visit, to sign and date the attached Informed Consent Form (see the last page). The signed Informed Consent Form will be kept in your medical notes, a copy will be given to you to keep, and a further copy will go in the hospital study file. If you do want to take part in the study, keep this Patient Information Sheet in case you need to read it in the future. We will write to your GP letting them know you are taking part in the study, and send them a copy of this information sheet too.

What will happen to me if I take part and what do I have to do?

Checking your blood sugar tests

If you agree to take part in the study and give your written informed consent, the Investigator Alastair will first check your most recent blood sugar results from clinic. If the most recent result was from a blood test taken some time ago, or if there was a possibility this previous blood test was taken when you had not avoided food and all drinks other than water from the night before (fasting), we may arrange for this to be repeated. You would need to come to clinic fasting, and have one teaspoon of blood taken. We will then arrange a date for you to come to clinic for your 30 minute visit. We will make sure the date and time suits you, fitting round work, holidays, and so on.

The visit

If you have been asked to have another blood sugar test, then on the day before your visit you will be asked to avoid eating from 10pm. You will also need to avoid most drinks after 10pm, although you will still be able to drink plain water freely, including the next morning. If you usually take your HIV medicine with food after you wake up, then as you normally do when being asked to fast for blood tests in clinic, you should delay taking your medicine, and bring it with you to clinic. We will give you breakfast once we have finished the test, and you can take your

medicine then. If you are having a blood test you will have a needle inserted into a vein in the crook of your elbow, and we will draw out a teaspoon of blood, in exactly the same way as you normally have blood drawn. If you have not been asked to have another blood sugar test you do not need to fast, and you can eat and take medicines as normal before coming to clinic.

We will be asking you some questions, and check with you that some information from your medical notes is correct and up to date. The information from your medical notes we will check includes social information such your ethnic background, HIV information including when you were first diagnosed and blood test results, relevant medical information including changes in body weight and shape, illnesses or conditions such as heart problems, and anti-HIV and other medicines used. We will ask you if anyone in your family has diabetes. We will measure your blood pressure, weight, height, waist, hips, and how much fat you have in your arms and legs. This visit will last about 30 minutes in total.

What will happen to my medical notes and who will see them?

Information will be taken from your medical notes at a time when they are not needed for your clinical care. Your direct healthcare team and the Investigator Alastair are the only people who may look at your medical notes for this study, and all of them will keep your identity confidential. At no stage will personal data such as your name or address be linked to the results that we get as you will always be identified by a code number only.

What will happen to any blood samples I give?

If you have a blood samples taken it will be used to measure blood sugar only and then destroyed.

What are the side effects of any treatment received when taking part?

For this study you are not being given any treatment at all.

What are the possible disadvantages and risks of taking part?

There is no additional risk to your health from taking part in this study. If you are asked to have a blood sugar test, a needle will be inserted so that we can take a blood sample, and this sometimes leads to local bruising and minor discomfort. The fasting blood test you might be asked to do means that you will go for up to 15 hours without eating, so you might feel a bit tired and hungry by the end of the test. We will give you breakfast as soon as the test is finished.

What are the possible benefits of taking part?

If we ask you to have a blood sugar test we might find this is a little high, or even that you have recently developed type 2 diabetes, and we would probably pick this up earlier than through normal clinic visits. You might also appreciate or benefit from some of the testing that is done as part of this study, for example measuring your weight and waist. We hope that the results of the study will be useful to the NHS and people living with HIV. If you take part in this study, you'll be helping us to learn more about the best ways to treat people living with HIV who are at risk of developing diabetes, and what risk factors to look out for.

What will happen if I don't want to carry on with the study after I've started?

Participation in this study is voluntary. Even if you agree to take part now, you are free to change your mind and withdraw from the study before or at the visit without affecting the standard of care that you receive. If you decide to withdraw from the study, any information already collected about you will remain anonymous and will not be used. The Investigator Alastair will check with you when you come for your visit to make sure you are happy, and consent to continue with the study.

If you decide not to take part, or if you decide to withdraw, you may be asked to take part in an interview to find out what you thought about the study, about any advice given, procedures involved, about any mistakes we might have made, and about how you feel about your health. These interviews will help us make research trials better in the future. However taking part in these interviews is entirely voluntary and it would be completely up to you to decide whether to take part or not.

Will I be paid to take part?

No. Taking part in this study is entirely voluntary. However if you are asked to fast and have a blood sugar test taken, we will provide you with a £3 breakfast voucher to use at the Hospital at the end of your visit.

What if there is a problem?

It is very unlikely that taking part in this study will cause you any problems. However, if you have a concern about any part of this study, you should ask to speak with your doctor or nurse who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the Patient Advice and Liaison Service (PALS) on the ground floor of the North Wing at St. Thomas' Hospital:

Patient Advice and Liaison Service ,KIC, Ground Floor, North Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, Tel: 020 7188 8801, Email: pals@gstt.nhs.uk

All staff involved hold professional indemnity to work within Guy's and St Thomas' NHS Foundation Trust. However in the unlikely event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Guy's and St. Thomas' NHS Foundation Trust, but you may have to pay your legal costs. The 24-hour contact number for formal NHS complaints at this St. Thomas' Hospital is 020 7188 8801.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. Your name and address will not be recorded for the purposes of the study; a code number will be used instead and you will not be identifiable by any other way in the study records. We will keep copies of your signed consent form in your medical notes and in a research file. This is completely separate from the information collected during the clinic visit and from your medical notes for the study, so there will be no way to link your identity to the study information.

Even though you will not be identifiable from them, the study records will be stored securely in a locked cabinet within locked premises under the control of the Chief Investigator, Alastair Duncan. Access to the study records and your medical notes, may be granted to appropriate people from the Trust Research and Development department, so that they can check that the study was carried out correctly. These people will treat information about you as strictly confidential. When the information is entered into a database on a computer for studying, this will be protected by a special password, and only accessible to the research team. The study records will be kept securely in this way for 5 years, in case we need to refer to them to answer questions about the study. At the end of this time, the study records will be disposed of securely in accordance with Guy's and St. Thomas NHS Foundation Trust policy.

What will happen to the results of the research study?

When the study is complete, the results will be written up by Alastair Duncan (the Chief Investigator for this study) and will be submitted for publication in medical journals and may be presented at medical conferences. You will not be identified in any report, publication or presentation. Your doctor will be able to tell you what the results of the study showed, if you are interested. Also your patient advocate will organise a patient forum to discuss the findings. If any abnormal or significant findings are found as part of your research visit, your GP and routine clinic doctor will be informed so they can review the information and action taken if necessary.

Who is organising and funding the research?

The study is sponsored by Guy's & St. Thomas' NHS Foundation Trust. It is funded by the Department of Health, through the National Institute for Health Research, and forms part of a PhD programme for the Investigator Alastair Duncan. Alastair has overall responsibility for this study, making sure that all procedures are followed correctly. His contact details are below.

Who has reviewed the study?
This study was given a favourable ethical opinion for conduct in the NHS on 12/11/2013 by the London-Bromley Research Ethics Committee.

This Participant Information Sheet is for you to keep.
Thank you for taking time to read the information.
Contact for further information:

Alastair Duncan (Research Dietitian)

Department of Nutrition and Dietetics
St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH
Study Phone: 07907 849626

Office Tel: 020 7188 2608 or 020 7188 2014

Email: alastair.duncan@gstt.nhs.uk

CONSENT FORM 1

Prevention of Type 2 Diabetes in HIV: RISK FACTORS (the "STOP Diabetes in HIV" study)

Name of Researcher with overall responsibility for the study: Alastair Duncan

	Please initial box
1. I confirm that I have read and understand the information sheet dated..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	☐
3. I understand that the study data will be stored securely for 5 years and disposed of securely at the end of this period.	☐
4. I agree to take part in the above study.	☐
5. I agree that relevant sections of my medical records will be looked at by a HIV research dietitian, nurse or doctor who will collect anonymised data where it is relevant to this study. I give permission for these researchers to have access to my records.	☐
6. I agree that any relevant material about me can be used in future research approved by an NHS Research Ethics Committee; I am aware this research may be in collaboration with a commercial company but that my identity will be kept anonymous.	☐
7. I agree to my GP being informed of my participation in this study.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

When completed photocopy twice: first copy for participant; second copy for researcher site file; and original to be kept in medical notes.

7.3 UK-SES Questionnaire

UK NATIONAL STATISTICS SOCIOECONOMIC CLASSIFICATION QUESTIONNAIRE

We are interested in finding out where you would be placed within a UK government method of measuring social standing. Please take your time to answer the following questions.

QUESTION 1: Have you have been out of work, retired, or a student for more than 6 months now? If so please go straight to question 10

Long-term unemployed ☐ Retired ☐ Student ☐

Questions 2-8 will ask about your job:
if you have more than one job choose the main one
if you have recently left work answer about your last job

QUESTION 2: Industry description

What does the firm/organisation you work for mainly make or do?

Question 3: Occupation title, current or last main job

What is your job?

Question 4: Occupation description, current or last main job

What did you mainly do in your job?

Question 5: Employee or self-employed

Were you working as an employee or were you self-employed?
Employee... ***Go to question 6***
Self-employed... Go to question 8

Question 6 (Employed only): Supervisory status

In your job, did you have any formal responsibility for supervising the work of other employees?

Yes ☐ No ☐

Question 7 (Employed only): Number of employees

How many people worked for your employer at the place where you worked? Were there...

1 to 24, 25 to 499, or 500 or more employees? ☐

NOW GO TO QUESTION 10...

Question 8 (Self-employed only): Self-employed working on own or with employees

Were you working on your own or did you have employees?

On own/with partner(s) but no employees ☐

With employees Go to question 9

Question 9 (Self-employed only): Number of employees (self-employed)

How many people did you employ at the place where you worked? Were there…

1 to 24, 25 to 499, or 500 or more employees? ☐

NOW GO TO QUESTION 10...

Question 10: Education

Did you take part in further education after school?

Yes ☐ No ☐

Question 11: Financial situation

How does the cost of living affect you?

Quite comfortably off ☐ Able to manage ☐

It's a strain to get by week by week

This is the end of the questionnaire.

7.4 Macarthur Subjective Socioeconomic Scale

Socioeconomic Status
In this questionnaire we are trying to find out where you place yourself within society. There are two questions to answer.

QUESTION 1:
Think of this ladder as representing where people stand **in their own communities**. At the top of the ladder are the people who have the highest standing in their community. At the bottom are the people who have the lowest standing in their community. People define community in different ways: please define it in whatever way is most meaningful for you.

Where would you place yourself on this ladder? Please place a large "X" on the rung where you think you stand at this time in your life, relative to other people in your community.

QUESTION 2:
Think of this ladder as representing where people stand **in the UK**. At the top of the ladder are the people who are best off – those who have the most money, the most education, and the most respected jobs. At the bottom are the people who are the worst off – those who have the least money, least education, and the least respected jobs or no job.

Where would you place yourself on this ladder? Please place a large "X" on the rung where you think you stand at this time in your life, relative to other people in the UK.

7.5 Standard Operating Procedure: Frequently Sampled Liquid Meal Tolerance Test

For the purpose of clinical research the Frequently Sampled Liquid Meal Tolerance Test may be used in place of the Oral Glucose Tolerance Test to measure the physiological response to a nutrient challenge in the fasting state. It is not standard practice to carry out such a procedure at Guy's and St Thomas' NHS Foundation Trust therefore this has been added.

Document name	The Frequently Sampled Liquid Meal Tolerance Test, Version 1.0
Effective from	January 2016 until January 2016
Author	Alastair Duncan, Lead Dietitian
Approved by, date	Professor Phil Chowienczyk
Supporting references	Maki et al (2010) DOI: 10.1089/dia.2010.0083

1. This Standard Operating Procedure (SOP) applies to personnel who will perform the Frequently Sampled Liquid Meal Tolerance Test (FSLMTT), and subsequently obtain samples from a peripheral venous cannula within the Clinical Research Facilities (CRF).

2. Personnel working in the CRF must use the same procedure when conducting a FSLMTT to ensure continuity and consistency of the procedure. As part of the FSLMTT peripheral venous cannulation is performed in order to provide access to the circulatory system. Multiple blood samples are obtained from this cannula to avoid repeated venepuncture.

3. The Oral Glucose Tolerance Test (OGTT) is routinely used in clinical practice for assessing the physiological response in the fasting state. The FSLMTT provides rich data compared to the OGTT. A mixed-nutrient liquid meal elicits a release of gut hormones and stimulated insulin release, providing a more physiologically accurate simulation. Secondly, frequent sampling post-meal allows the researcher to observe the response more closely over time.

4. The CRF Manager must ensure that relevant CRF personnel are trained in this SOP

5.1 In advance of the procedure subjects will have been advised of the following:
• For 48 hours in advance eat moderately portioned carbohydrate-containing meals three times per day and avoid strenuous exercise and smoking
• Fast for 12 hours prior to attending for the procedure, although water is permitted.

5.2 In advance of this procedure the Investigator or other delegated individual must check with the participant regarding any previous problems with phlebotomy or cannula insertion.

5.3 The participant should be sitting comfortably in a chair

5.4 The Investigator is responsible for inserting a peripheral venous cannula. This duty can be delegated to other appropriately qualified members of the research team who:
• Have attended the Trust mandatory venepuncture training course.
• Are deemed competent by an appropriately trained member of the CRF Management Team
• Have updated their Training Record File and are on the study log.

5.5 The delegated individual must perform the procedure in accordance with the Trust relevant Health and Safety Policy for Peripheral venous cannulation

5.6 The delegated individual is responsible for ensuring that blood is obtained from a cannula according to the protocol. This duty can be delegated to other appropriately qualified staff.

5.7 The delegated individual must ensure the correct participant is identified and cross referenced with appropriate blood request forms.

5.8 The delegated individual will ensure all study/trial specific documentation is prepared, any local blood request forms are completed, and the correct blood bottles are labelled.

5.9 The delegated individual will explain the procedure to the participant.

5.10 The delegated individual must keep accurate records regarding:

- The length, gauge of the cannula
- Date and time of insertion, number and location of attempts
- Identification of the site
- Name and person placing the device
- Type of dressing
- Patients tolerance of the device

5.11 Before and after each element of the procedure the delegated individual must wash their hands in accordance with Trust policy, and wear the appropriate protective clothing.

5.12 The delegated individual will prepare all equipment required including sharps bin, Vacutainer Luer connector Blue, Vacutainer bottles / study/trial specific blood kits / Vacutainer Shield, Mediswab, non-sterile gloves and trolley, 10 ml Plastipak syringe x2 (1 for flush, 1 for 4ml blood draw), 0.9% normal saline (check expiry date), Smartsite needle-free valve port

5.13 The delegated individual must prepare the working environment to ensure comfort, light, room to manoeuvre, position and privacy of the patient.

5.14 Following insertion of the cannula the delegated individual must check the cannula site for swelling or redness. Check that the appropriate dressing has been used. If redness or swelling is identified around the cannula site, the cannula should be removed and re-sited.

5.15 The delegated individual must attach a smartsite needle-free valve port if the cannula does not already have one attached. This is achieved by screwing the clear section of the smartsite onto the end of the cannula. The smartsite needle-free port must be cleaned with an alcohol wipe. The smartsite connector should be allowed to dry for approximately one minute.

5.16 The delegated individual must draw up 1-2 mls of 0.9% normal saline using a sterile Plastipak syringe, and flush the cannula to prevent blood from clotting and confirm patency.

5.17 The delegated individual must withdraw 4mls of blood from the cannula in a Plastipak 10ml syringe and discard as clinical waste. Discarding this sample will ensure accurate analysis of the results and will also remove any residual saline from the previous flushing.

5.18 Baseline blood samples should be drawn, with time accurately recorded, as follows:
• The delegated individual must use a blue Vacutainer leur connector and attach it to the Vacutainer shield, remove the white cover of the tip to expose the grey sheath of the needle and screw mechanism, screw the tip onto the Vacutainer shield, remove the blue cover from the Vacutainer tip, and place the leur lock connector into the white section of the smartsite.
• The delegated individual must then use the appropriate blood bottles as specified in the study/trial protocol. Order of draw instructions may be specified in the study/trial protocol.
• For a standard frequently sampled liquid meal tolerance test a minimum of one tube each for glucose (fluoride oxalate) and insulin (clotted serum) should be drawn

5.19 The delegated individual must place the blood bottle into the Vacutainer sheath. Slight force may be required. Once the connection is made the blood will begin to flow.

5.20 The delegated individual must ensure that all sharps are disposed of immediately into a sharps container in accordance with the Trust Waste Policy, must wash their hands in accordance with the Trust Hand Hygiene Policy, and flush as outlined in 5.16

5.21 The delegated individual must gently invert the specimens to mix if they contain an additive or as dictated by the study/trial protocol.

5.22 The liquid meal should be given to the participant to drink and consumed within 2 minutes. When the participant consumes the last of the 200g, the time should be recorded, and this time will dictate when samples should be drawn for the remainder of the test.

5.23 Samples should be drawn at the following times post liquid meal: 5, 10, 15, 30, 60, 90, 120, 150, 180 minutes
5.24 At each time point the procedures outlined in 5.17 to 5.21 should be repeated, with flushing as in 5.16 completed at the end of each blood draw

5.25 If any blood spillage occurs the delegated individual should clean up the spillage

5.26 An appropriately trained individual must remove the cannula when no longer indicated. The time and date the cannula was removed must be documented in the source data. The state of the site should be recorded in source data.

5.27 The delegated individual must dispose of the cannula as per the Waste Policy.

5.28 The delegated individual will ensure all procedures for samples outlined in the study/trial protocol are followed.

5.29 The delegated individual must ensure that samples shipped off site are prepared, stored and couriered according to protocol requirements.

7.6 Stool and Symptom Questionnaire

FUNCTIONAL GUT SYMPTOM EVALUATION: Baseline, Monthly & End of Study

Participant ID _____ **Date:** _____

1. **Do you currently have any problems with your stomach or bowels?** (Circle one)

   Yes No

2. **Please rate your stomach or bowel symptoms during the last week by placing a tick in the box that best describes each symptom**
   (Please tick the "none" box if you do not have this symptom)

	No symptoms or very rarely None	Occasional or mild symptoms Mild	Frequent symptoms that affect some social activities Moderate	Continuous symptoms that affect most social activities Severe
Abdominal pain/discomfort	☐	☐	☐	☐
Abdominal bloating/distension	☐	☐	☐	☐
Increased flatulence/wind	☐	☐	☐	☐
Belching or burping	☐	☐	☐	☐
Stomach/abdominal gurgling	☐	☐	☐	☐
Urgency to open bowels	☐	☐	☐	☐
Incomplete evacuation (feeling of inability to pass all stool)	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Heartburn	☐	☐	☐	☐
Acid regurgitation	☐	☐	☐	☐
Tiredness/lethargy	☐	☐	☐	☐
Overall symptoms	☐	☐	☐	☐

3. **Currently, how often do you pass a bowel action?** (please tick one box)

Once a week	☐
Once every 4-6 days	☐
Once every 2-3 days	☐
Once a day	☐
2-3 times a day	☐
4-6 times a day	☐
7 or more times a day	☐

4. **Please tick the box that best describes your current stool:**

Bristol Stool Chart

Type 1	Separate hard lumps, like nuts (hard to pass)	☐
Type 2	Sausage-shaped but lumpy	☐
Type 3	Like a sausage but with cracks on its surface	☐
Type 4	Like a sausage or snake, smooth and soft	☐
Type 5	Soft blobs with clear-cut edges (passed easily)	☐
Type 6	Fluffy pieces with ragged edges, a mushy stool	☐
Type 7	Watery, no solid pieces. **Entirely Liquid**	☐

5. **Thinking about what you eat and drink at the moment, and any medicines you take, do any of these affect your stomach or bowels?**

6. **Any other comments about your stomach or bowels?**

7.7 Interview Topic Guides

Interview Topic Guide 1: Decliners

Introduce self, make sure participant is comfortable and have what they need, remind participant of consent process and confidentiality, remind participant that honest answers are important / they are the expert, they can decline answering individual / particular questions.
Is there anything they want to ask before starting the recording?
SWITCH ON RECORDERS
Briefly explain the purpose of interview:

We want to find out what people think about the STOP Diabetes in HIV study.
Although this is about the diabetes in HIV study, we could start with a general chat.
Can you tell me what's happening in your life right now? Typical day?
What's easy and what's hard in your life right now?
How long have you been living with HIV?

STOP DIABETES IN HIV

Before hearing about the study:

How long have you known you are borderline diabetic? How did you feel?
How did you hear about the study?

The study itself:

How did you feel when we / you and Alastair first started talking about the study?
Participant Information Sheet
What sounded good / not so good?
Anything that wasn't explained properly?

Can you tell me why you decided not to take part in the 6 month intervention study?

Most people need to change what they eat, do more physical activity, and lose a few inches around their tummy to help bring down their blood sugar.
How do you feel thinking about this? How do you feel about your body shape?

Is there anything about living with HIV that made you think twice about taking part?
If I was to start from scratch and redesign the study, what would make it better?
Were the monthly visits enough or too frequent?
Is there anything that would make it easier/harder to make changes to eating/activity?

How do you feel now after deciding not to do the study?
How do you feel about your body shape now?
What are you going to do in the next few months?
Is there anything else you'd like to tell me about the diabetes in HIV study?

RESEARCH IN THE CLINIC

Have you taken part in research here or elsewhere before?
Can you tell me about what's good / not good about research here?
What are the Participant Information Sheets like for other studies?
How do you feel about the support you get in research studies?
Is there anything that would make research studies better for you?
Is there anything else you'd like to say about research in general?

Ok that's us getting towards the end now. Is there anything else you'd like to say?
How was this interview for you?
If you remember something later on that you wish you'd said you can always contact me
THANK YOU VERY MUCH FOR YOUR TIME
I'll now switch off the recorders.

Interview Topic Guide 2: Withdrawers

Face to face interview: participants who did not complete the intervention.

Introduce self, make sure participant is comfortable and have what they need, remind participant of consent process and confidentiality, remind participant that honest answers are important / they are the expert, they can decline answering individual / particular questions.
Is there anything they want to ask before starting the recording?
SWITCH ON RECORDERS
Briefly explain the purpose of interview:

We want to find out what people think about the STOP Diabetes in HIV study.
Although this is about the diabetes in HIV study, we could start with a general chat.
Can you tell me what's happening in your life right now? Typical day?
What's easy and what's hard in your life right now?
How long have you been living with HIV?

STOP DIABETES IN HIV

Before hearing about the study:
How long have you known you are borderline diabetic? How did you feel?
How did you hear about the study?
The study itself:
How did you feel when we / you and Alastair first started talking about the study?
Participant Information Sheet
What sounded good / not so good?
Anything that wasn't explained properly?

Can you tell me why you decided to take part in the 6 month intervention study?

Most people need to change what they eat, do more physical activity, and lose a few inches around their tummy to help bring down their blood sugar.
How do you feel thinking about having to make these changes?
How do you feel about your body shape at the moment?
Is there anything about living with HIV that made you think twice about taking part in the study?
If I was to start from scratch and redesign the study, what would make it more appealing for you?
Were the monthly visits enough or too frequent?
Is there anything that would make it easier / harder to make changes to eating / activity?

OK now let's talk about how you feel today. How do you feel after NOT completing the study?
How do you feel about your body shape now?
What are you going to do in the next few months?
Is there anything else you'd like to tell me about the diabetes in HIV study?

RESEARCH IN THE CLINIC
Have you taken part in research here or elsewhere before?

Tell me about the research studies you have taken part in.
Can you tell me about what's good / not so good about research here?
What are the Participant Information Sheets like for other studies?
How do you feel about the support you get in research studies?
Is there anything that would make research studies better for you?
Is there anything else you'd like to say about research in general?

Ok that's us getting towards the end now. Is there anything else you'd like to say?
How was this interview for you?
If you remember something later on that you wish you'd said you can always contact me
THANK YOU VERY MUCH FOR YOUR TIME
I'll now switch off the recorders.

Interview Topic Guide 3: Completers

Face to face interview: participants who completed the intervention.

Introduce self, make sure participant is comfortable and have what they need, remind participant of consent process and confidentiality, remind participant that honest answers are important / they are the expert, they can decline answering individual / particular questions.
Is there anything they want to ask before starting the recording?

SWITCH ON RECORDERS

Briefly explain the purpose of interview:
We want to find out what people think about the STOP Diabetes in HIV study.
Although this is about the diabetes in HIV study, we could start with a general chat.
Can you tell me what's happening in your life right now? Typical day?
What's easy and what's hard in your life right now?
How long have you been living with HIV?

STOP DIABETES IN HIV

Before hearing about the study:
How long have you known you are borderline diabetic? How did you feel?
How did you hear about the study?
How did you feel when we / you and Alastair first started talking about the study?
Participant Information Sheet
What sounded good / not so good?
Anything that wasn't explained properly?

Can you tell me why you decided to take part in the 6 month intervention study?
Most people need to change what they eat, do more physical activity, and lose a few inches around their tummy to help bring down their blood sugar.
How do you feel thinking about having to make these changes?
How do you feel about your body shape at the moment?
Is there anything about living with HIV that made you think twice about taking part in the study?
If I was to start from scratch and redesign the study, what would make it more appealing for you?
Were the monthly visits enough or too frequent?
Is there anything that would make it easier / harder to make changes to eating / activity?
What happened during the six months…
Can you tell me what it was like to take part?
What was it like on the first day at the Clinical Research Facility?

3-hour blood test? Questionnaires?
Did you get enough information to go away with on that first day?

How were the first few months?
Level of support you received?
Spacing of the visits?
Reminder texts and calls?

Changes you make to eating…
What changes did you make in your diet?
What foods did you enjoy changing?
Anything in particular that made it easier or harder to make these changes to eating?
Food samples at the end of the first month – useful or not so useful?
Do you think changing what you were eating had any effect on your shopping?

Changes you made to physical activity…
Did you start doing more physical activity?
How useful was the pedometer?
Is there anything in particular that made it easier or harder to make these changes to activity?

How do you feel now after completing the full 6 months of the study?
Probe: What impact has it had on you?

How do you feel about your body shape now?
What are you going to do in the next few months?
Are there any challenges to keeping up the diet and activity changes?
Probe: Do you want to keep up these changes?

If we were to redesign the study from scratch…
Is there anything else you'd like to tell me about the diabetes in HIV study?

RESEARCH IN THE CLINIC
Have you taken part in research here or elsewhere before?
Tell me about the research studies you have taken part in.
Can you tell me about what's good / not so good about research here?
What are the Participant Information Sheets like for other studies?
How do you feel about the support you get in research studies?
Is there anything that would make research studies better for you?
Is there anything else you'd like to say about research in general?

Ok that's us getting towards the end now. Is there anything else you'd like to say?
How was this interview for you?
If you remember something later on that you wish you'd said you can always contact me
THANK YOU VERY MUCH FOR YOUR TIME
I'll now switch off the recorders.

7.8 Intervention Food Samples

A range of foods was offered to participants at their visit on Day 30. The aim was to provide samples to try foods new to participants, or known but untested. The range included low salt, reduced sugar and reduced fat foods, oily fish, wholegrains, sweeteners and monounsaturated fat-rich cooking oils.

7.9 Images of Gay Men who Self-identify as Bears

Stock images of gay men who self-identify as bears. These are not photographs of study participants. They are presented to help the reader unfamiliar with the gay community visualise the identity of men who self-identify as bears. Source: Internet free licence.